In the United States Court of Federal Claims

OFFICE OF SPECIAL MASTERS

Filed: August 29, 2022

HOANG-HOA NGUYEN, as Special Administrator for the Estate of TUYET MAI,	*	PUBLISHED
Petitioner,	*	No. 17-2051V
v.	*	Special Master Nora Beth Dorsey
SECRETARY OF HEALTH AND HUMAN SERVICES,	*	Entitlement; Tetanus-Diphtheria-Acellular Pertussis ("Tdap") Vaccine; Stevens-Johnson Syndrome ("SJS"); Toxic Epidermal Necrolysis ("TEN"); Drug Reaction with Eosinophilia and Systemic Symptoms ("DRESS") Syndrome; Severe Cutaneous Adverse Reaction ("SCAR").
Respondent.	*	

Howard Scott Gold, Gold Law Firm, Wellesley, MA, for Petitioner.
Naseem Kourosh, U.S. Department of Justice, Washington, DC, for Respondent.

DECISION[1]

I. INTRODUCTION

On December 28, 2017, Hoang-Hoa Nguyen, as Special Administrator for the Estate of Tuyet Mai ("Ms. Mai"), ("Petitioner") filed a petition for compensation under the National Vaccine Injury Compensation Program ("Vaccine Act" or "the Program"), 42 U.S.C. § 300aa-10

[1] Because this Decision contains a reasoned explanation for the action in this case, the undersigned is required to post it on the United States Court of Federal Claims' website in accordance with the E-Government Act of 2002. 44 U.S.C. § 3501 note (2012) (Federal Management and Promotion of Electronic Government Services). **This means the Decision will be available to anyone with access to the Internet.** In accordance with Vaccine Rule 18(b), Petitioner has 14 days to identify and move to redact medical or other information, the disclosure of which would constitute an unwarranted invasion of privacy. If, upon review, the undersigned agrees that the identified material fits within this definition, the undersigned will redact such material from public access.

et seq. (2012).[2] Petitioner alleges that Ms. Mai suffered Toxic Epidermal Necrolysis ("TEN"), serum sickness-like illness, toxic shock syndrome, Stevens-Johnson Syndrome ("SJS"), allergic exfoliative dermatitis, and subsequently died as a result of a tetanus-diphtheria-acellular pertussis ("Tdap") vaccine she received on August 11, 2015.[3] Petition at Preamble (ECF No. 1). Respondent argued against compensation, stating that "this case is not appropriate for compensation under the [Vaccine] Act." Respondent's Report ("Resp. Rept.") at 2 (ECF No. 15).

This is a very tragic case and the undersigned extends her sympathy to Ms. Mai's family for their loss. However, after carefully analyzing and weighing the evidence presented in accordance with the applicable legal standards, the undersigned finds that Petitioner has failed to provide preponderant evidence that Ms. Mai's Tdap vaccine caused her to suffer SJS/TEN, or any other severe cutaneous adverse reaction ("SCAR"), or caused her death. Thus, Petitioner has failed to satisfy her burden of proof under Althen v. Secretary of Health & Human Services, 418 F.3d 1274, 1280 (Fed. Cir. 2005). Accordingly, the petition shall be dismissed.

II. ISSUES TO BE DECIDED

The parties dispute both diagnosis and causation. Regarding diagnosis, Petitioner's expert, Dr. M. Eric Gershwin, opines that Ms. Mai's appropriate diagnosis was SJS/TEN, while Respondent's expert, Dr. Markus Boos, opines that the correct diagnosis was drug reaction with eosinophilia and systemic symptoms ("DRESS") syndrome. Petitioner's Exhibit ("Pet. Ex.") 11-A at 1-2; Resp. Ex. A at 6-7.

As for causation, Petitioner alleges that Ms. Mai's condition and subsequent death were caused by the Tdap vaccination administered on August 11, 2015. Pet. Motion for Ruling on the Record ("Pet. Mot."), filed Sept. 16, 2021, at 1 (ECF No. 91). Respondent disagrees and asserts that Petitioner has failed to prove the Althen criteria by preponderant evidence. Resp. Response to Pet. Mot. ("Resp. Response"), filed Nov. 1, 2021, at 24-35 (ECF No. 92). Additionally,

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[2] The National Vaccine Injury Compensation Program is set forth in Part 2 of the National Childhood Vaccine Injury Act of 1986, Pub. L. No. 99-660, 100 Stat. 3755, codified as amended, 42 U.S.C. §§ 300aa-10 to -34 (2012). All citations in this Decision to individual sections of the Vaccine Act are to 42 U.S.C. § 300aa.

[3] The petition also alleges that Ms. Mai's Tdap vaccine "significantly aggravated" her allergic exfoliative dermatitis. Petition at 1. However, none of the expert reports or subsequent briefing discuss significant aggravation. Petitioner's motion for a ruling on the record alleges the decedent's conditions were only "caused-in-fact" by the vaccine at issue. Pet. Motion for Ruling on the Record ("Pet. Mot."), filed Sept. 16, 2021, at 1 (ECF No. 91). Therefore, this Decision does not include a significant aggravation analysis using the Loving elements. Loving v. Sec'y of Health & Hum. Servs., 86 Fed. Cl. 135, 142-44 (2009). However, even if the undersigned conducted a Loving analysis, Petitioner would not have been able to satisfy Loving Prongs four and five for the same reasons the undersigned found Petitioner was not able to satisfy Althen Prongs one and two, as described in more detail below.

Respondent asserts that another drug, allopurinol, is the alternative cause of Ms. Mai's condition. Id. at 35-37.

III. BACKGROUND

A. Medical Terminology

"Drug-induced severe cutaneous adverse reactions (SCARs) include . . . drug reaction with eosinophilia and systemic symptoms (DRESS) and epidermal necrolysis (Stevens-Johnson Syndrome [SJS], toxic epidermal necrolysis [TEN])." Pet. Ex. 13-B at 1.[4] "The identification of the causal drug is crucial in order to avoid further exposure, but making the right differential diagnosis of the type of SCAR is equally important since treatment, follow-up, and prognosis of different SCARs are not the same" and "sometimes the early distinction . . . can be extremely challenging." Id.

1. Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis

SJS and TEN "form a spectrum of rare, but severe and potentially fatal, mucocutaneous diseases, characterized by widespread epidermal necrosis and mucosal involvement" due to death of keratinocytes, the prominent cell type in the epidermis. Pet. Ex. 11-C at 2-3.[5] The two conditions, SJS and TEN, are thought to be "essentially the same disease" but differ "according to the extent of detached [] epidermis, expressed as a percentage of the total body surface area." Id. at 2. "In SJS, epidermal loss affects less than 10% of the [total body surface area], whereas TEN involves greater than 30% of the [total body surface area]." Id.

Approximately 80% of TEN cases are thought to be caused by medications. Pet. Ex. 11-C at 2. Both SJS and TEN involve "a specific immune response to one or more drugs, constituting a form of delayed-type hypersensitivity." Id. "More than 100 drugs of various classes have been associated with SJS and TEN," including the medication allopurinol.[6] Id. at 5. The most "suspicious" time frame for considering a "specific drug as the causative factor is a delay of between 4 and 28 days between initial dosing of the medication and onset of symptoms. For most high risk drugs . . . , the risk of developing SJS or TEN is elevated only during the initial two months of use." Id.

There is a "prodromal phase of SJS and TEN" which "frequently consists of influenza [("flu")]-like symptoms, including fever, cough, myalgias, arthralgias, and malaise, which may last from one day to two weeks. This is followed by the appearance of skin lesions, mostly on

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[4] Aneline Casagranda et al., Overlapping DRESS and Stevens-Johnson Syndrome: Case Report and Review of the Literature, 9 Case Reps. Dermatology 1 (2017).

[5] Andrea T. Borchers, Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis, 7 Autoimmunity Revs. 598 (2008). Dr. Gershwin is one of the named authors.

[6] Allopurinol is prescribed to reduce uric acid. Allopurinol, Dorland's Med. Dictionary Online, https://www.dorlandsonline.com/dorland/definition?id=1854 (last visited Aug. 11, 2022).

the trunk and face, but [the lesions] can also occur on the neck and proximal extremities." Pet. Ex. 11-C at 5. The characteristic rash is "flat, irregular" with "atypical target lesions or diffuse purpuric macules that frequently have necrotic centers (particularly in TEN), and tend to coalesce over the course of time." Id. Due to cell death, "the epidermis detaches from the dermis, giving rise to flaccid blisters." Id. In the majority of cases, the mucous membranes are involved. Id. Involvement of the eyes is often seen, with conjunctivitis, edema, and corneal ulcers. Id. Additional complications may include "sloughing of the epithelium of [the] trachea, bronchi, or the gastrointestinal tract." Id. "Sloughing of the bronchial epithelium" may cause severe hypoxia, "necessitat[ing] mechanical ventilation and carr[ying] a poor prognosis." Id.

There are a number of conditions in the "differential diagnosis" for SJS/TEN. Pet. Ex. 11-C at 5. The illness is generally a clinical diagnosis, confirmed by biopsy which "classically shows widespread keratinocyte apoptosis[7] and full-thickness epidermal necrosis and detachment, while the underlying dermis is not greatly altered." Id. at 5-6. Treatment consists of withdrawing the offending drug and supportive care. Id. at 6. The mortality of TEN is approximately 30 to 50% of patients during the acute phase of the condition. Id. The "most frequent cause[] of death [is] [] sepsis and multi-organ failure." Id. at 7.

2. Drug Reaction with Eosinophilia and Systemic Symptoms Syndrome

DRESS syndrome is "a rare, potentially life-threating adverse drug reaction with cutaneous manifestations and internal organ involvement." Resp. Ex. A, Tab 5 at 2.[8] It is caused by a "severe hypersensitivity to a medication and its reactive drug metabolites." Id. Many different medications have been implicated, including allopurinol. Id. at 3 tbl.1.

"DRESS syndrome usually begins within [two] months" after taking the offending medication, and most often within two to six weeks after initiation of the medication. Resp. Ex. A, Tab 5 at 3. The symptoms, however, may begin sooner, and can be "more severe upon reexposure." Id. While the etiology is not known, there is thought to be a genetic predisposition. Id. In addition to a genetic component, "an immunologic mechanism is also widely believed" to play a role in the cause of DRESS syndrome. Id. at 3-4.

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[7] Keratinocyte is "an epidermal cell that synthesizes keratin; about 95 percent of the cells of the epidermis are of this type." Keratinocyte, Dorland's Med. Dictionary Online, https://www.dorlandsonline.com/dorland/definition?id=26829 (last visited Aug. 11, 2022). Apoptosis is "a morphologic pattern of cell death affecting single cells, marked by shrinkage of the cell, condensation of chromatin, formation of cytoplasmic blebs, and fragmentation of the cell into membrane-bound apoptotic bodies that are eliminated by phagocytosis." Apoptosis, Dorland's Med. Dictionary Online, https://www.dorlandsonline.com/dorland/definition?id=3806 (last visited Aug. 11, 2022).

[8] Zain Husain et al., DRESS Syndrome: Part I. Clinical Perspectives, 68 J. Am. Acad. Dermatology 693e.1 (2013).

The illness "often begins with prodromal symptoms of pruritus[9] and pyrexia,"[10] followed by "cutaneous manifestations," including a "morbilliform rash."[11] Resp. Ex. A, Tab 5 at 5. The rash "is characterized by a diffuse, pruritic, macular, and occasionally erythrodermatous exanthema,"[12] which "usually first involves the face, upper aspect of the trunk, and upper extremities, and later spreads to the lower extremities, becoming infiltrative and indurated with associated edema." Id. There may be facial edema, around the eyes. Id. "Approximately 25% of patients have prominent facial swelling . . . ." Id. Over time, the rash evolves, and appears violet in color, "with diffuse scaling." Id. A skin biopsy commonly reveals "dense, perivascular lymphocytic infiltrate in the papillary dermis, with the presence of extravasated erythrocytes, eosinophils, and dermal edema. This infiltrate is generally denser than other drug reactions. Eosinophils may be present, which are thought to cause direct toxic damage to tissues . . . ." Id. at 8-9.

In DRESS syndrome, there may be multiple organ involvement in "the lymphatic, hematologic, and hepatic systems, followed by renal, pulmonary, and cardiac manifestations." Resp. Ex. A, Tab 5 at 5. "The liver is the most frequently affected visceral organ in DRESS syndrome, often with varying degrees of hepatitis." Id. at 6. "Liver abnormalities with elevated serum alanine aminotransferase (ALT) are found in approximately 70% of patients . . . . The elevated liver enzymes may persist for several days after withdrawal of the culprit drug, but may sometimes take months to completely resolve." Id. at 7. The kidneys may also be affected. Id. Allopurinol is one of the most commonly "offending drugs associated with kidney injury." Id.

There are no definitive criteria or standards for the diagnosis of DRESS syndrome. Resp. Ex. A, Tab 5 at 9. "Clinical testing and biopsy can be helpful, but are not always specific." Id. Proposed criteria include findings of eosinophilia and atypical lymphocytes. Id. at 9-10. Treatment includes withdrawal of the offending medication, corticosteroids, and supportive care.

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[9] Pruritus is another word for itching. Pruritus, Dorland's Med. Dictionary Online, https://www.dorlandsonline.com/dorland/definition?id=41580 (last visited Aug. 11, 2022).

[10] Pyrexia means fever. Pyrexia, Dorland's Med. Dictionary Online, https://www.dorlandsonline.com/dorland/definition?id=42394 (last visited Aug. 11, 2022).

[11] Morbilliform is "like measles; resembling the eruption of measles." Morbilliform, Dorland's Med. Dictionary Online, https://www.dorlandsonline.com/dorland/definition?id=32145 (last visited Aug. 11, 2022).

[12] Erythroderma is an "abnormal redness of the skin, usually meaning that it is over widespread areas of the body," also called exfoliative dermatitis. Erythroderma, Dorland's Med. Dictionary Online, https://www.dorlandsonline.com/dorland/definition?id=17229 (last visited Aug. 11, 2022). Exanthem is a rash or "a disease in which skin eruptions or rashes are a prominent manifestation." Exanthem, Dorland's Med. Dictionary Online, https://www.dorlandsonline.com/dorland/definition?id=17730 (last visited Aug. 11, 2022).

Resp. Ex. A, Tab 4 at 2.[13] Most patients recover; however, there is "an estimated mortality of 10%, primarily because of hepatic necrosis." Id. at 8. Septic shock due to complications caused by bacterial or fungal infections has been reported as a significant cause of death. Id.

B. Procedural History

Petitioner filed a petition on December 28, 2017, and medical records were filed in February 2018. Petition; Pet. Exs. 3-9. On October 5, 2018, Respondent filed his Rule 4(c) Report, arguing against compensation. Resp. Rept. at 2.

On March 15, 2019, Petitioner filed a letter from Ms. Mai's treating physician, Dr. Peter Nguyen. Pet. Ex. 10. Petitioner filed an expert report from Dr. Gershwin on May 26, 2019, and additional medical records on August 6, 2019. Pet. Exs. 11-A, 12. Respondent filed expert reports from Dr. Boos and Dr. You-Wen He on September 12, 2019. Resp. Exs. A, C.

Thereafter, this case was reassigned to the undersigned. Notice of Reassignment dated Oct. 7, 2019 (ECF No. 27). A Rule 5 conference was held on October 30, 2019. Order dated Nov. 4, 2019 (ECF No. 28). Thereafter, the parties discussed informal resolution of this case but were unsuccessful. Id. at 3; Joint Status Rept., filed July 21, 2020 (ECF No. 45). During a status conference on August 4, 2020, the undersigned and parties discussed whether to resolve this matter through a hearing or a ruling on the record, and the parties agreed to resolve this case through a ruling on the record. Order dated Aug. 4, 2020 (ECF No. 46).

Petitioner filed a supplemental expert report from Dr. Gershwin on September 22, 2020 and updated medical records in January and March 2021. Pet. Exs. 13-19. Additional records were filed by both parties in April and May 2021. Pet. Exs. 20-23; Resp. Exs. E-G. On June 14, 2021, Respondent filed a supplemental expert report from Dr. Boos. Resp. Ex. H.

Petitioner filed her motion for a ruling on the record on September 16, 2021. Pet. Mot. Respondent filed his response on November 1, 2021, and Petitioner filed his reply on November 7, 2021. Resp. Response; Pet. Reply to Resp. Response ("Pet. Reply"), filed Nov. 7, 2021 (ECF No. 93).

The undersigned held a status conference on December 17, 2021. Order dated Dec. 17, 2021 (ECF No. 97). "After reviewing all of the evidence, including medical records, expert reports, medical literature, and the parties' briefs, the undersigned explained that she has questions which are currently making it difficult for her to decide the issue of entitlement." Id. at 1. "The undersigned discussed the issues making it difficult for her to render a decision, including the factual issues regarding the nature of the rash, onset, and whether there are photographs of the decedent's rash." Id. The undersigned and parties discussed holding an entitlement hearing or obtaining additional information by affidavits, photographs, and possible supplemental expert reports in lieu of a hearing. Id. The parties indicated that they preferred a ruling on the record. Joint Status Rept., filed Jan 6, 2022 (ECF No. 100).

[13] Zain Husain et al., DRESS Syndrome: Part II. Management and Therapeutics, 68 J. Am. Acad. Dermatology 709e.1 (2013).

Thereafter, Petitioner filed a declaration, photographs of Ms. Mai, and a supplemental expert report from Dr. Gershwin. Pet. Exs. 24-25. Respondent filed a supplemental expert report from Dr. Boos on March 1, 2022. Resp. Ex. I. In April 2022, the parties filed supplemental briefs. Pet. Memorandum ("Pet. Mem."), filed Apr. 4, 2022 (ECF No. 108); Resp. Response to Pet. Supplemental Brief ("Resp. Supp. Br."), filed Apr. 20, 2022 (ECF No. 109).

This matter is now ripe for adjudication.

C. Factual History

1. Summary of Medical Records

a. Relevant Medical History Prior to Vaccination

Prior to the vaccination at issue, on May 13, 2014, Ms. Mai complained of "itchiness around eyes." Pet. Ex. 18 at 2. It does not appear that any diagnosis was made regarding her complaint of itchiness around the eyes. On March 3, 2015, Ms. Mai again complained of "itching around the eyes." Pet. Ex. 4 at 24. No assessment was documented regarding this complaint, however, her medications included Besivance[14] and Bepreve.[15] Id.

On June 18, 2015, Ms. Mai again complained of an itchy rash around her eyes to her primary care physician, Dr. Peter L. Nguyen.[16] Pet. Ex. 4 at 20. Physical examination revealed that Ms. Mai had slight erythema (redness) around her eyes and a dry macular rash on her arms and legs. Id. There was no swelling or discharge. Id. At that same visit, Ms. Mai was noted to have an elevated serum uric acid (8.3). Id. Dr. Nguyen diagnosed her with gout. Id. He also diagnosed allergic conjunctivitis and diabetes mellitus with renal manifestations. Id. Dr. Nguyen prescribed allopurinol 300 mg daily for the gout. Id. Pharmacy records indicated that Ms. Mai filled the prescription for allopurinol on the same day, June 18, 2015, and she received 90 pills (three month supply). Pet. Ex. 23 at 3.

Ms. Mai returned to see Dr. Nguyen on August 6, 2015, now complaining of an itchy rash to her face. Pet. Ex. 4 at 19. Dr. Nguyen described the rash on her face as a "vascular rash." Id. There was "no swelling," no bleeding, and no discharge. Id. Dr. Nguyen diagnosed

[14] Besivance is prescribed to treat bacterial conjunctivitis, or pink eye. Besivance, https://www.besivance.com/ (last visited Aug. 11, 2022).

[15] Bepreve is "indicated for the treatment of itching associated with allergic conjunctivitis." Bepreve, https://www.beprevepro.com/ (last visited Aug. 11, 2022).

[16] There are several different physicians named Dr. Nguyen. Going forward, all references to Dr. Nguyen are for Dr. Peter L. Nguyen.

her with dermatitis and prescribed triamcinolone acetonide ("TAC")[17] 0.1% cream twice daily. Id.

b. Vaccination

On August 11, 2015, then age 75, Ms. Mai received the Tdap vaccination at issue here.[18] Pet. Ex. 3 at 1; Pet. Ex. 12 at 1; Pet. Ex. 20 at 3. At the time of vaccination, Ms. Mai's records show that her past medical history was significant for type II diabetes, hypertension, elevated cholesterol, dementia, and positional dizziness. Pet. Ex. 4 at 12, 21-24, 28.

c. Summary of Medical Records After Vaccination

Just over two weeks after vaccination, on August 27, 2015, Ms. Mai presented to Dr. Nguyen, complaining of a fever for two days. Pet. Ex. 4 at 18. She felt "tired," reported decreased energy, and had "no cold tolerance." Id. Dr. Nguyen documented a macular rash, with no swelling, and no discharge. Id. He did not document the location of the rash, how long it had been present, or any other characteristic features of it. See id. Diagnoses were fever that was improved, fatigue, dermatitis, and chronic kidney disease. Id. Laboratory studies were ordered, and Ms. Mai was instructed to take Benadryl for her itching, and to return in one week to review her laboratory studies. Id.

Ms. Mai returned for follow up on September 2, 2015, complaining of diarrhea for one day, with no fever, chills, nausea, or vomiting. Pet. Ex. 4 at 17. She also complained of "rash all over." Id. Dr. Nguyen described the rash as a "macular rash throughout body with slight edema." Id. He noted her recent vaccinations. Id. The previous laboratory studies revealed abnormal glomerular filtration rate (GFR 34), abnormal liver functions studies (ASR 356, ALT 306), and abnormal urinalysis (positive for leukocytes, glucose, and protein). Id. Uric acid was in the normal range at 4.9. Id. Dr. Nguyen diagnosed Ms. Mai with elevated liver function tests, gastroenteritis, chronic kidney disease, diabetes mellitus type II, and an allergic reaction, possibly secondary to vaccination. Id. He put her simvastatin[19] on hold, ordered repeat bloodwork, and instructed her to take Benadryl, presumably for itching. Id. She was to return for follow up in one week, or sooner if needed. Id.

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[17] Triamcinolone acetonide is "applied topically to the skin or oral mucosa as an anti-inflammatory." Triamcinolone Acetonide, Dorland's Med. Dictionary Online, https://www.dorlandsonline.com/dorland/definition?id=114887 (last visited Aug. 11, 2022).

[18] Ms. Mai also received a Zostavax vaccination on August 11, 2015. Pet. Ex. 12 at 1; Pet. Ex. 20 at 3. Zostavax is not a covered vaccine under the Vaccine Act. Petitioner has not alleged any injury due to the Zostavax vaccine. See Petition; Pet. Mot.

[19] Simvastatin is "used to lower blood lipid levels in the treatment of hypercholesterolemia and other forms of dyslipidemia and to reduce the risk of morbidity and mortality associated with atherosclerosis and coronary heart disease." Simvastatin, Dorland's Med. Dictionary Online, https://www.dorlandsonline.com/dorland/definition?id=45888 (last visited Aug. 11, 2022).

Later that day, on September 2, 2015, Ms. Mai was taken by ambulance to the emergency department ("ED") at the Regional Medical Center of San Jose. Pet. Ex. 19 at 943. The ambulance First Responder Worksheet documented "[r]edness x 10 days" and "itchy." Id. at 942. Ms. Mai also complained of diarrhea for two days, rash with itching, and weakness. Id. at 943. Ms. Mai's home medications were documented, but allopurinol was not identified in the medications listed.[20] Id. at 944, 1112. Several of her medications were identified as "unknown." Id. at 1112. The emergency room narrative note stated the

> [patient's] family . . . called 911 after the [patient] [] presented with a rash that has spread over the past nine days to entire body. . . . [Patient] got a shot at a Walgreens store ten days ago and then began to present with small penny sized rashes to her face and anterior torso. The rash grew over the next week . . . .

Id. at 945.

The nursing triage note stated that per the EMS report, Ms. Mai had generalized weakness and diarrhea. Pet. Ex. 19 at 839. She had received "a 'shot' from Walgreens 10 days ago[21] then got some rashes to arm. Now [patient] has gen[eralized] red rash all over her body." Id. The nurse observed that Ms. Mai was alert, and had a generalized red rash all over her body and face ("red rash from head to toe"), but that "[she] denie[d] feeling itchy." Id. at 839, 841. She also complained of abdominal pain. Id. at 841. Initial diagnoses were severe sepsis and rash. Id. at 839.

An ED note authored by Dr. David Nguyen on the night of September 2, 2015 stated Ms. Mai

> present[ed] to ED with a worsening rash that developed about 9-10 days ago after receiving two vaccinations. . . . [R]ash [] started with her hands and abdominal area [and] has spread diffusely throughout the body. . . . [H]ad intermittent fevers when the rash started. . . . [R]ash appeared to be much worse today. . . . Upon arrival to the ED, patient does have a diffuse rash with purpura in the lower extremity region as well as a diffuse bright red erythematous rash throughout the upper body and face. Patient does have some skin peeling around the mouth area. No obvious intraoral lesions. . . . Primary concern was for Severe Sepsis with end organ dysfunction (no specific source of infection yet) and possible early [SJS] with this rash.

Pet. Ex. 19 at 836-37. Ms. Mai was admitted to the intensive care unit ("ICU") for further care and evaluation. Id. at 837.

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[20] The listed medications were HCTZ (hydrochlorothiazide), metformin, Zocor, Cozaar, Aricept, aspirin, Simvador, Lopressor, and Januvia. Pet. Ex. 19 at 944.

[21] On September 2, 2015, Certified Physician Assistant Kathryn Weber wrote Ms. Mai "[h]ad tetanus and [] zoster [vaccinations] 10 days ago, then rash started next day." Pet. Ex. 19 at 829.

History and physical examination were documented by Dr. Sarah F. Sanghavi on September 3, 2015. Pet. Ex. 7 at 67-69. Under history of present illness, Dr. Sanghavi stated that Ms. Mai, age 75, presented to the emergency room with

> 5 days of rash. The patient notes that approximately nine days ago she received her [Tdap] vaccination. About 4 days later, she developed a salmon colored blanching rash that began on her trunk and extended to her arms and legs and face. She states the rash was initially pruritic, but is no longer. Associated symptoms were a sore throat for which she took 2 days of antibiotics . . . . The rash preceded the use of antibiotics.

Id. at 67. Ms. Mai was described as "acutely ill." Id. Laboratory results revealed an elevated white blood cell count of 21.6. Id. at 68.

Dr. Sanghavi's physical examination revealed no mouth lesions. Pet. Ex. 7 at 68. Dr. Sanghavi described Ms. Mai's rash as "a confluent blanching salmon colored rash over her trunk, upper extremities and lower extremities extending to her feet, sparing the palms and soles. It takes on a morbilliform quality in her thighs and legs." Id. There were "[n]o areas of desquamation[,] [n]o vesicles or scale[,] . . . [and] no mucosal involvement." Id.

Regarding diagnosis, Dr. Sanghavi's assessment was "rash, elevated [liver function tests,] and acute kidney injury." Pet. Ex. 7 at 68. Specifically, she diagnosed Ms. Mai with

> [r]ash with systemic symptoms. The differential include[d] infection versus a serum sickness type reaction versus drug rash with eosinophilia and systemic symptoms (DRESS). The rash . . . appears to be either a drug reaction, immune complex reaction, or an exanthem. . . .
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> The patient does not have any lesions of oral mucosa or desquamation that would be typical for [SJS]. In addition, she does have eosinophilia which is also not typical of [SJS]. . . . [S]he has not had any introduction of new medications within the last 2 to 6 weeks that would fit the time course for DRESS.

Id. at 68-69. While Dr. Sanghavi questioned whether Ms. Mai had a drug reaction, no specific medication was identified as the offending agent.

Dr. Alex Studemeister, infectious disease specialist, performed a consult on September 3, 2015. Pet. Ex. 19 at 852. He wrote, "possible reaction to recent vaccination." Id. Also on September 3, 2015, a progress note by Dr. Ravi K. Aggu-Sher noted that the rash had an "[u]nclear etiology. ? from recent vaccinations." Id. at 853.

A skin biopsy was performed on Ms. Mai's right arm on September 3, 2015, which was interpreted as "spongiosis, perivascular lymphohistiocytic infiltrate with eosinophils and focal interface changes." Pet. Ex. 19 at 961-62 (emphasis omitted). Differential diagnoses "include[d] drug eruption, spongiotic dermatitis such as [] allergic dermatitis, contact dermatitis, atopic dermatitis, ID reaction[], as well as pityriasis rosea." Id. at 962. There was "[n]o evidence of

vasculitis," and the biopsy was "negative for fungal organisms." Id. Urine culture revealed *Escherichia coli* ("*E. coli*"),[22] but blood cultures showed no growth. Id. at 973-74. Stool specimen was negative for Shiga toxin, ova and parasites, and *Clostridium difficile*. Id. at 975-76.

On September 4, 2015, Ms. Mai was seen by Dr. Ahmet H. Lavkan. Pet. Ex. 19 at 858. Dr. Lavkan noted that a workup was in progress and that "mucous membranes are spared [negative for [SJS]]." Id. at 861. He also noted that "Group A strep antigen was negative," that the rash did not "appear bacterial," and that Ms. Mai had "[n]o signs of toxic shock." Id. He further noted "[d]ifferential is broad but at the top comes allergic reaction to the vaccine she received or the components of it." Id. Dr. Lavkan saw Ms. Mai the next day, September 5, 2015. Id. at 854. Her "[r]ash [was] improved" and "[s]he [was] now clinically stable." Id. Under impression, Dr. Lavkan documented Ms. Mai's rash was a "[p]robable allergic reaction to recent vaccine." Id. at 856. Ms. Mai was transferred from the ICU to the medical surgical floor. Id. at 857.

Ms. Mai was seen by infectious disease specialist, Dr. Studemeister, again on September 6, 2015. Pet. Ex. 19 at 872. Dr. Studemeister noted Ms. Mai had a "possible reaction to recent vaccination, improving." Id. at 873. He also diagnosed "possible concurrent [urinary tract infection], *E. coli* in urine culture." Id. (emphasis added).

The next day, September 7, Ms. Mai was discharged. Pet. Ex. 7 at 65. Dr. Zheng Gang Zhang documented the discharge diagnoses, which included "[s]evere dermatitis, most likely reaction to the vaccine." Id. Ms. Mai's medications at the time of discharge did not include allopurinol.[23] See id. at 66.

After discharge, Ms. Mai followed up with Dr. Nguyen on September 9, 2015. Pet. Ex. 4 at 11. Ms. Mai reported that her rash was slowly improving, and that she had itching. Id. The rash was described as macular rash throughout her body. Id. Ms. Mai returned to Dr. Nguyen on September 23, 2015, and complained that she still had the rash over her body. Id. at 10. Dr. Nguyen prescribed Atarax for itching and prednisone 20 mg twice daily. Id.

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[22] *Escherichia coli* is "a common facultative organism of the intestines" that can "produc[e] fevers and diarrhea . . . . The fever-causing strains are found in urinary tract infections, abscesses, conjunctivitis, and occasionally septicemic conditions . . . . Shiga toxin-producing groups (STEC, formerly called enterohemorrhagic, or EHEC) cause acute bloody diarrhea and hemolytic-uremic syndrome." Escherichia Coli, Dorland's Med. Dictionary Online, https://www.dorlandsonline.com/dorland/definition?id=73835 (last visited Aug. 11, 2022).

[23] Based on a review of Ms. Mai's medication administration records from September 3 to 7, 2015, it does not appear that she was administered allopurinol during this hospital admission. See Pet. Ex. 19 at 990-1011.

On September 29, 2015, Ms. Mai saw a dermatologist,[24] Dr. Mychael Luu, complaining that her skin was "peeling all over [her] body." Resp. Ex. E at 1. Dr. Luu noted an abnormal reaction on the abdomen and left cheek, and diagnosed a "TEN like reaction with widespread scaling erythroderma most likely [seco]ndary to vaccination, either shingles or tetanus vaccine, with systemic involvement of at least liver and kidney." Id. Ms. Mai's medication list that day at Dr. Luu's office did not include allopurinol. See id.

Ms. Mai next saw Dr. Huy A. Nguyen, a gastroenterologist, on October 16, 2015 for elevated liver function tests. Resp. Ex. G at 71. She complained of weakness and fatigue, and her skin was described as "very dark." Id. Her medication list that day included allopurinol 300 mg. Id. Physical examination revealed that she appeared ill and had dark skin. Id. at 71-72. Impression was fatigue, abnormal weight loss, and abnormal liver tests. Id. at 72. Dr. Huy Nguyen opined that Ms. Mai's liver dysfunction was likely "drug, shock, or sepsis related." Id. He questioned whether she had "toxic shock syndrome or possible [SJS]." Id.

Ms. Mai returned to see Dr. Huy Nguyen on October 30 for follow up. Resp. Ex. G at 87. At this visit, he documented that her skin rash was "not significantly improving" and that "[s]he started having more itching." Id. Her medication list that day again included allopurinol 300 mg. Id.

Several days later, on November 2, 2015, Ms. Mai had a follow up visit with her primary care physician, Dr. Nguyen. Pet. Ex. 4 at 3. She complained of an "itchy rash all over," described by Dr. Nguyen as a "macular rash to torso/arms/legs & face." Id. Diagnosis was urticaria. Id. Dr. Nguyen prescribed prednisone and Atarax for itching. Id. Ms. Mai returned to see Dr. Nguyen on November 23, for a follow up of her rash. Id. at 2. She reported that her "rash improved, but [was] not resolved." Id. Dr. Nguyen refilled Ms. Mai's prescription for allopurinol, with a quantity of 30 pills. Pet. Ex. 23 at 4.

Ms. Mai returned to see Dr. Nguyen on December 14, 2015, again complaining of an "itchy rash all over." Pet. Ex. 4 at 1. She also had elevated liver function tests. Id. Dr. Nguyen ordered prednisone 10 mg twice daily. Id.

Ms. Mai's condition continued to deteriorate and on December 19, 2015, she again presented to the ED at Regional Medical Center of San Jose. Pet. Ex. 19 at 9, 21. History[25] was provided by her family, who reported that she had a

> worsening rash that developed [a] few days ago. Patient had a similar episode of this in the past, 2 months ago . . . . Onset of similar symptoms initially was after a

[24] This appears to be the first and only time Ms. Mai was seen by a dermatologist.

[25] History documented by Dr. Erica Timiraos McEnery also noted that "patient had a similar appearing rash at the beginning of September . . . after receiving vaccinations," and "[s]he developed severe skin sluffing[] and severe dermatitis at the time requiring ICU admission. Pet. Ex. 19 at 27. Dr. McEnery also stated Ms. Mai "improved dramatically after being treated with steroids and reportedly [] had a skin biopsy at the time which was inconclusive." Id. at 27-28.

> tetanus shot and herpes zoster vaccine. Patient was treated and got better but did not completely recover. Per family, rash suddenly appeared again a few days ago and has been worsening and spreading diffusely throughout. Per family, also reports chills, weakness, and decreased appetite.

Id. at 21. Physical examination revealed "[p]urulent drainage around [the] eyes," "[d]ry mucous membranes," raw and cracking lips, and "diffuse scaly skin sluffing rash." Id. at 23. Ms. Mai had been unable to eat due to involvement of her mucous membranes. Id. at 28. Differential diagnoses included "severe dermatitis versus [SJS] given mucous membrane involvement." Id.

Due to the unavailability of dermatology services at Regional Medical Center of San Jose, plans were made to transfer Ms. Mai; however, there were no beds available at another hospital. Pet. Ex. 19 at 28. The ED physician, Dr. Erica Timiraos McEnery, discussed the case with a dermatologist at another hospital "who reviewed photos of the patient's rash and state[d] it was not consistent with [SJS] and believe[d] it [was] exfoliative dermatitis."[26] Id. Ms. Mai was admitted for treatment of dehydration and urinary tract infection. Id. Her reported medications on admission to the hospital did not include allopurinol. Id. at 22, 37. No allergies were noted on December 19, 2015, but by December 21, an allergic reaction of severe rash to both the zoster and Tdap vaccines were noted. Id. at 22, 38.

Admitting history and physical examination by Dr. Padmashri K. Srinivasa noted "significant conjunctival edema in both eyes and significant edema in the left upper eyelid." Pet. Ex. 7 at 6-7. Ms. Mai had a "desquamating rash all over her body with only palms being spared, but involving the soles of the feet." Id. at 7. Diagnoses included sepsis, urinary tract infection, and exfoliative dermatitis. Id. at 8. Dr. Srinivasa explained that it was not possible to transfer Ms. Mai to a "higher level of care for . . . dermatology and rheumatology consult" because there were no beds available. Id. "The ED physician [] spoke with the dermatologist from Valley [hospital], who upon seeing photographs texted of the patient diagnosed the patient with exfoliative dermatitis." Id.

An infectious disease consult was done on December 21, 2015 by Dr. Michael T. Charney for Ms. Mai's severe skin rash and fever. Pet. Ex. 19 at 44-45. Dr. Charney described Ms. Mai's history and stated that she had been

> doing well for the past 2 months up until 5 days before admission with rash all over her body. It is unclear if she has had any recent new medication. She is on multiple medications at home, but apparently nothing new . . . . The only allergy we can document is Tdap [and] herpes zoster vaccine. She has a generalized

[26] Exfoliative dermatitis, also called erythroderma, is "a scaly erythematous dermatitis over wide areas of the skin, sometimes with loss of hair and nails, hyperkeratosis of palms and soles, pruritus, or other severe, debilitating physiologic effects." Exfoliative Dermatitis, Dorland's Med. Dictionary Online, https://www.dorlandsonline.com/dorland/definition?id=69267 (last visited Aug. 11, 2022). Exfoliative dermatitis "may be a secondary or reactive process accompanying an underlying cutaneous disorder such as atopic dermatitis or psoriasis, or it may be a primary or idiopathic disorder." Id.

> erythematous rash, swelling of the face, blisters, which are now drying up. . . . Her mouth shows swelling of the lips and also inflammation of the tongue with stomatitis. . . . The skin shows some peeling, it is dry. . . . [I]t looks as though she did have some blisters that have now dried up.

Id. at 44. A urine culture showed *E. coli*, which was being treated with antibiotics. Id. Ms. Mai was also receiving intravenous methylprednisolone. Id. at 45. Dr. Charney's diagnosis was "[SJS]/erythema, multiforme, etiology unclear" and "[a]cute cystitis due to *E. coli*." Id. (emphasis added).

On January 1, 2016, while being assisted back to bed, Ms. Mai "developed sudden onset weakness" that "progressed rapidly to [a] syncopal episode." Pet. Ex. 19 at 46. She became unresponsive, and a code blue was called. Id. She regained consciousness, and was transferred to the ICU, where she required vasopressors and intensive supportive care. Id. at 46-47. Assessment was septic shock, acute respiratory failure, liver dysfunction with transaminitis and elevated alkaline phosphatase, thrombocytopenia attributable to underlying liver disease in addition to septic shock, acute kidney dysfunction secondary to sepsis and shock, and exfoliative allergic dermatitis. Id. at 48. She was subsequently intubated, her condition worsened, and she died on January 2, 2016. Id. at 51-52.

Based on a review of the medication administration records for Ms. Mai's hospital admission from December 19, 2015 to January 2, 2016, it does not appear that she was given allopurinol during this hospital admission. See Pet. Ex. 19 at 388-437, 439-63.

Blood culture drawn on January 1, 2016 was positive for *Staphylococcus epidermidis*. Pet. Ex. 7 at 44.

Death certificate identified the immediate cause of death as cardiac arrest, circulatory shock, disseminated intravascular coagulopathy, and an *E. coli* urinary tract infection, along with other significant conditions contributing to death including liver dysfunction, metabolic and lactic acidosis, respiratory failure, diabetes mellitus type II, and exfoliative dermatitis. Pet. Ex. 8 at 1.

2. Declaration of Petitioner, Daughter of Ms. Mai[27]

Petitioner, Hoang-Hoa Nguyen, is the daughter of the decedent, Ms. Mai. Pet. Ex. 24 at ¶ 1. She addressed two issues in her declaration. The first relates to the medication allopurinol. Petitioner stated that Ms. Mai would usually begin taking prescription medication once she received it from the pharmacy. Id. at ¶ 2. Ms. Mai also "typically follow[ed] medical advice from her physicians." Id. at ¶ 3. Petitioner "ha[d] no recollection of [her] mother ever taking [a]llopurinol." Id. at ¶ 4. On September 2, 2015, when the emergency medical technicians ("EMTs") came to Ms. Mai's home to provide emergency care, one of the EMTs requested her

[27] The exhibit is titled "Affidavit of Hoang-Hoa Nguyen" but it is not notarized, and therefore, the undersigned references it as a declaration.

medications, collected them from her nightstand, and took all of the medications with him on the ambulance. Id. at ¶¶ 6-7.

The second issue addressed by Petitioner's declaration relates to the rash that Ms. Mai had before vaccination as compared to the rash after vaccination. Petitioner stated that "in the spring/early summer of 2015," Ms. Mai had "a mild macular rash that was occasional and typically resulted from eating larger amounts of seafood in the same day. It bore no resemblance to the rash she developed after her vaccination in August 2015." Pet. Ex. 24 at ¶ 8. Petitioner also authenticated and explained the photographs of Ms. Mai that have been filed. Id. at ¶¶ 9-12 (citing Pet. Exs. 24-A to D). A pre-vaccination photograph was taken in July 2015. Id. at ¶ 9 (citing Pet. Ex. 24-A). Three other photographs were taken after vaccination, approximately September 17, September 19, and December 21, 2015, respectively. Id. at ¶¶10-12 (citing Pet. Exs. 24-B to D).

3. Letter by Dr. Peter L. Nguyen

Petitioner filed a letter authored by Ms. Mai's primary care physician, Dr. Nguyen, dated March 12, 2019. Pet. Ex. 10 at 1. The letter states that "Ms. [] Mai's rash that was noted on June 18, 2015 and August 6, 2015 was of a different character and nature than that which developed after her vaccination of August 11, 2015. It is my medical opinion that the pre-vaccination macular rash and her post-vaccine reaction are unrelated." Id.

D. Expert Reports

1. Petitioner's Expert, Dr. M. Eric Gershwin[28]

a. Background and Qualifications

Dr. Gershwin is board certified in internal medicine, rheumatology, and allergy and clinical immunology. Pet. Ex. 11-B at 2. Since obtaining his M.D. from Stanford University in 1971 and completing an internship and residency, he has been a professor in rheumatology and allergy and the Director of the Allergy-Clinical Immunology Program at the University of California School of Medicine in Davis, California. Id. at 1-2. Throughout his career, he has won various awards and honors, served as an editor, reviewer, or member on journals, and co-authored or authored over 1,000 publications. Id. at 4-123. Dr. Gershwin "ha[s] seen and treated patients with [SJS] and [TEN] for nearly 40 years." Pet. Ex. 11-A at 1. He has also published on SJS and TEN. Id. (citing Pet. Ex. 11-C).

b. Opinion

i. Diagnosis

As a prelude to his opinion, Dr. Gershwin summarized Ms. Mai's medical history and clinical course. See Pet. Ex. 11-A at 1-2. He noted that her prior medical history was significant

[28] Petitioner filed three expert reports by Dr. Gershwin. Pet. Exs. 11-A, 13, 25-A.

for "hypertension, [elevated] lipids, dizziness, dementia[,] and type II diabetes." Id. at 1. On June 18, 2015, Ms. Mai was diagnosed with hyperuricemia[29] for which she was prescribed allopurinol. Id. Dr. Gershwin opined that Ms. Mai "did not have any untoward reactions to the allopurinol, but was noted to have an itchy rash near and around her eyes on August 6, 2015, that was diagnosed as dermatitis." Id. Notably, "there was no swelling and no other evidence of epithelial cell involvement." Id. Dr. Gershwin also observed that there was no indication of any progression of this eye rash in Ms. Mai's medical records. Id.

On August 11, 2015, Ms. Mai received a Tdap vaccination. Pet. Ex. 11-A at 1. Dr. Gershwin noted that on August 27, 2015, she returned to her primary care provider, Dr. Nguyen, who noted that Ms. Mai had a "macular rash without swelling." Id. She also complained of a fever for two days. Id. Diagnosis was dermatitis. Id. Dr. Gershwin observed that Dr. Nguyen, "did not comment that the rash had gotten any worse. However, on September 2, 2015, Ms. Mai returned to her primary care physician because of a one day history of diarrhea and a diffuse rash. The rash was noted to be throughout her body, was macular, with some edema." Id. Dr. Nguyen questioned "whether she had an allergic reaction to the vaccination." Id.

The next day, September 3, 2015, Ms. Mai was admitted to Regional Medical Center of San Jose. Pet. Ex. 11-A at 1. "[T]he hospital records reported that the rash had begun on August 15, 2015, or four days after the Tda[p] vaccine." Id. Ms. Mai had a sore throat, fever, and elevated white blood cell count (21,600). Id. She reported that the rash was itchy. Id. On September 7, 2015, she was discharged "with a diagnosis of severe dermatitis, most likely reaction to the vaccine." Id. Ultimately, Ms. Mai saw a dermatologist, Dr. Luu, who diagnosed "an adverse drug reaction – [TEN], possibl[y] secondary to vaccination for shingles and tetanus." Id. at 1-2.

Dr. Gershwin explained that "Ms. Mai's rash persisted [and] she developed exfoliation, and was ultimately admitted to the hospital on December 19, 2015." Pet. Ex. 11-A at 2. She developed complications, including urinary tract infection and liver dysfunction. Id. "On January 1, 2016, she became unresponsive and ultimately died of cardiac arrest, circulatory shock, disseminated intravascular coagulation, and an *E. [c]oli* urinary tract infection." Id. (emphasis added). While her death was associated with her underlying medical conditions, Dr. Gershwin opined that it "stem[ed] directly from her development of exfoliative dermatitis and the diagnosis of [TEN]." Id.

In his second expert report, Dr. Gershwin addressed the issue of diagnosis more directly. He provided the reasons for his opinion that Ms. Mai had TEN and not DRESS, which Respondent's expert, Dr. Boos, asserts was the appropriate diagnosis. Pet. Ex. 13 at 1. First, Dr. Gershwin noted that one of Ms. Mai's treating physicians, a dermatologist, diagnosed her with TEN. Id. Specifically, on September 29, 2015, a dermatologist documented that she had a rash, with peeling all over her body, that was characterized as TEN-like. Id. (citing Resp. Ex. E at 1).

[29] Hyperuricemia is the "excess of uric acid or urates in the blood." Hyperuricemia, Dorland's Med. Dictionary Online, https://www.dorlandsonline.com/dorland/definition?id=24061 (last visited Aug. 11, 2022).

Second, Dr. Gershwin opined that Ms. Mai had "organ failure and systemic features," as well as "systemic inflammatory disease" secondary to TEN, which he opined is a "disease more severe than DRESS." Pet. Ex. 13 at 1. Dr. Gershwin also noted that a poor prognosis is more consistent with TEN than DRESS. Id.

Next, Dr. Gershwin opined that onset was "more than eight weeks after initiation of allopurinol,"[30] which he believed was less consistent with a diagnosis of DRESS. Pet. Ex. 13 at 1. In support of this point, Dr. Gershwin cited several articles that describe the latency period between initiation of the offending medication and onset in cases of DRESS. Mockenhaupt[31] stated "DRESS is characterized by a long latency (two to eight weeks) between drug exposure and disease onset." Pet. Ex. 13-D at 1. Similarly, Wolf et al.[32] reported a delayed onset of three to eight weeks. Pet. Ex. 13-E at 1. Another article by Casagranda et al., however, stated that DRESS occurred approximately two to six weeks after initiation of the offending drug. Pet. Ex. 13-B at 2.

According to Dr. Gershwin, "[t]he most common cause of [SJS] and [TEN] is allopurinol."[33] Pet. Ex. 11-A at 2. He explained, "[h]owever, the risk of getting these syndromes [is] overwhelming[ly] found within the first 8 weeks of beginning the allopurinol." Id. Dr. Gershwin noted that "Ms. Mai was prescribed the allopurinol on June 18, 2015" and then developed the "salmon colored blanching rash" on August 15, 2015, which he opined "appears to be beyond 8 weeks."[34] Id.

His next argument was that SJS/TEN and DRESS are very similar and may even be overlapping conditions. Pet. Ex. 13 at 2. He cited an article by Casagranda et al., in which the authors note that while DRESS and SJS/TEN are different conditions, in some cases, "the early distinction . . . can be extremely challenging, and overlapping conditions could therefore be taken into consideration." Pet. Ex. 13-B at 1. The authors also noted that "[s]ometimes these

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[30] Ms. Mai filled her prescription for allopurinol on June 18, 2015. See Pet. Ex. 23 at 3 (pharmacy records). Assuming that she began taking the medication that day, and that her rash began on August 15, 2015, onset was 58 days, or eight weeks and two days. See Pet. Ex. 11-A at 1 (agreeing the rash began four days post-vaccination, or on August 15, 2015); Pet. Ex. 7 at 67 (noting onset of rash was four days after vaccination).

[31] Maja Mockenhaupt, Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS), UpToDate, https://www.uptodate.com/contents/drug-reaction-with-eosinophilia-and-systemic-symptoms-dress (last updated Apr. 8, 2020).

[32] Ronni Wolf et al., Drug Rash with Eosinophilia and Systemic Symptoms vs Toxic Epidermal Necrolysis: The Dilemma of Classification, 23 Clinics Dermatology 311 (2005).

[33] Borchers et al. notes a study that found that allopurinol to be the most common medication known to cause SJS/TEN, especially when prescribed at a dose greater than 200 mg daily. Pet. Ex. 11-C at 5. Ms. Mai was prescribed 300 mg daily. Pet. Ex. 4 at 20; Pet. Ex. 23 at 3.

[34] This time frame is 58 days, or eight weeks and two days.

entities can share some features, raising the hypothesis of overlap syndromes." Id. at 2. They reported a case of an 86-year-old female whose illness was probably triggered by allopurinol, and who met the criteria for both SJS and DRESS. Id. at 2-3.

In another article cited by Dr. Gershwin, authored by Kim et al.,[35] the authors emphasized the "clinical similarities" between SJS/TEN and DRESS, all defined as SCARs. Pet. Ex. 25-E at 1. The similarities "can cause confusion in diagnosis, leading to delays in proper management." Id. In the case reported in Kim et al., the patient had started treatment with anti-tuberculosis medication (isoniazid, rifampicin, ethambutol, and levofloxacin), and seven weeks later presented with a maculopapular rash on her truck and extremities and lesions in her mouth. Id. The medication was discontinued and steroids were administered. Id. She improved, but on day 11 of her hospitalization, she deteriorated and her earlier presentation (consistent with SJS) changed, and she met the criteria for DRESS. Id. She required high dose steroids, hemodialysis, and a prolonged hospitalization. Id. The authors concluded that the patient presented with SJS, but was ultimately diagnosed with DRESS, caused by ethambutol. Id. at 2. Even with extensive laboratory results and clinical information, the authors concluded that it was "difficult to determine" whether the patient had "SJS-DRESS overlap or DRESS from the beginning . . . . However, it is clinically meaningful to recognize that there are some cases of SCARs that have mixed features." Id.

In another article authored by Wolf et al.,[36] the authors addressed the same concerns expressed by Kim et al. See Pet. Ex. 25-H. In Wolf et al., the patient met the criteria for diagnosis of both SJS and DRESS. Id. at 3. The authors concluded that "[a] case that precisely fits the definition of two syndromes that have different characteristics, different treatments, and different prognoses indicates that there is a fault in the classification." Id. "[A]ny classification will essentially be descriptive, and therefore intrinsically flawed, as there is a degree of overlap between the clinical manifestation of these conditions." Id.

Similarly, Magbri and Seth[37] noted that SJS, TEN, and DRESS "have many histological and biological features in common. Diagnosis of these syndromes is mainly based on clinical grounds, and overlap between the various clinical entities do occur[,] making accurate diagnosis

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[35] Ju-Young Kim et al., A Case of Drug Reaction with Eosinophilia and Systemic Symptoms Induced by Ethambutol with Early Features Resembling Stevens-Johnson Syndrome, 93 Acta Dermato-Venereologica 753 (2013).

[36] Ronni Wolf et al., Drug Rash with Eosinophilia and Systemic Symptoms Versus Stevens-Johnson Syndrome – A Case That Indicates a Stumbling Block in the Current Classification, 141 Int'l Archives Allergy & Immunology 308 (2006).

[37] Awad Magbri & Harshit Seth, Drug Rash with Eosinophilia and Systemic Symptoms (DRESS) or Stevens-Johnson Syndrome (SJS): Does the Name Matter!, 3 J. Clinical Nephrology & Renal Care 23 (2017).

on clinical grounds almost impossible." Pet. Ex. 25-F at 1. Teraki et al.[38] likewise noted "there is confusion in the diagnosis of []DRESS syndrome vs. [SJS]/[TEN]." Pet. Ex. 25-G at 1.

Where there is a question of diagnosis, Dr. Gershwin believes that a patient "should be classified as having SJS/TEN and not as having DRESS."[39] Pet. Ex. 13 at 2. In support of this point, he cited an article by Wolf et al., where the authors "presented arguments for and against including patients with skin lesions of the SJS/TEN syndromes who also have fever (practically all of the patients) and internal organ involvement (most of the patients) under the definition of DRESS syndrome." Pet. Ex. 13-E at 1. They "conclude[d] that it ma[de] more sense for patients with SJS/TEN to be classified as such and not be lumped together under the misleading label of DRESS syndrome." Id.

DRESS was characterized as a "syndrome [] defined by the triad of fever, dermatitis, and internal organ involvement, characteristically occurring with a delay of 3 to 8 weeks after the initiation of the first treatment with the culpable drug." Pet. Ex. 13-E at 1. "The skin is the most commonly involved organ in DRESS, with a very wide spectrum of manifestations and severity, starting from a faint generalized exanthematous eruption to [SJS] or [TEN]." Id. The authors explained that "[a]ccording to contemporary vernacular, when the cutaneous manifestations of DRESS syndrome are those of SJS or TEN, the condition is defined as 'DRESS syndrome with severe cutaneous reactions.'" Id. The authors disagreed with this approach, instead arguing that "whenever SJS/TEN are present, they dominate the clinical picture and dictate our approach and actions, so why not . . . define the syndrome according to its most significant pathology." Id. at 3.

Lastly, Dr. Gershwin cited to a "report of a patient who developed DRESS as a result of allopurinol," where "the authors suggested that [the illness] occurred only because it had been triggered by [the] [flu] vaccine." Pet. Ex. 13 at 2. The Solak et al.[40] authors thought that the "viral antigens in the vaccine [] might have contributed to trigger the disease." Pet. Ex. 13-C at 2. However, they were unable to do requisite testing to explore their theory. Id. Therefore, they did not reach any conclusion as to the role of the patient's flu vaccination. Id.

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[38] Y. Teraki et al., Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis Due To Anticonvulsants Share Certain Clinical and Laboratory Features with Drug-Induced Hypersensitivity Syndrome, Despite Differences in Cutaneous Presentations, 35 Clinical & Experimental Dermatology 723 (2009).

[39] In the Casagranda et al. case report, the patient fulfilled the criteria for DRESS and SJS, and was considered an overlapping case. Pet. Ex. 13-B at 1. The authors could not identify the culprit drug with any certainty, but they suspected allopurinol, due to the fact that it is implicated in a large proportion of drug reactions. Id. at 4.

[40] Berna Solak et al., DRESS Syndrome Potentially Induced by Allopurinol and Triggered by Influenza Vaccine, 2016 BMJ Case Reps. 1. Although Dr. Gershwin's cite to the Solak et al. article and comment suggests that allopurinol and the vaccine may together have combined to trigger illness, he did not develop this theory.

Based on the diagnoses of Ms. Mai's treating physicians, the medical records, medical literature, an onset greater than eight weeks after initiation of allopurinol, as well as the fact that Ms. Mai's clinical course was characterized by organ failure and a poor prognosis, Dr. Gershwin opined that "Ms. Mai suffered, more likely than not, from TEN, . . . secondary to her vaccination." Pet. Ex. 13 at 2.

ii. Althen Prong One

Dr. Gershwin explained that SJS/TEN "is a specific immune response to a foreign agent, which leads to a severe delayed-type hypersensitivity reaction." Pet. Ex. 11-A at 2. The offending agents "are predominately medication-induced." Id. The damage to the epidermis is caused by keratinocyte apoptosis. Id. He further explained that the specific mechanisms are not well understood, but the most current explanation is that "drug-specific CD8+ cytotoxic T cells[41] utilizing perforin/granzyme B[42] trigger keratinocyte apoptosis." Id. The apoptosis may expand due to "the interaction of either membrane-bound or soluble Fas ligand (sFasL) with its receptor Fas."[43] Id. Peripheral lymphocytes and keratinocytes may play a role in this process. Id. "Cytokines produced by T lymphocytes, macrophages[,] or keratinocytes may participate by

[41] CD8 cells are "T lymphocytes that carry the CD8 antigen." CD8 Cells, Dorland's Med. Dictionary Online, https://www.dorlandsonline.com/dorland/definition?id=64001 (last visited Aug. 11, 2022). Cytotoxic T cells are "differentiated T lymphocytes that can recognize and lyse target cells bearing specific antigens recognized by their antigen receptors. . . . The cytotoxic activity requires firm binding of the lymphocyte to the target cell to produce holes in the plasma membrane of the target cell, loss of its cell content, and osmotic lysis." Cytotoxic T Lymphocytes, Dorland's Med. Dictionary Online, https://www.dorlandsonline.com/dorland/definition?id=87555 (last visited Aug. 11, 2022).

[42] Perforin is "a protein expressed by cytotoxic lymphocytes and forming a transmembrane pore at the site of target cell lysis." Perforin, Dorland's Med. Dictionary Online, https://www.dorlandsonline.com/dorland/definition?id=37681 (last visited Aug. 11, 2022).

[43] "Fas [] is a member of the tumor necrosis factor (TNF) receptor superfamily. Fas ligand (FasL) is a member of the TNF family of type 2 membrane proteins. . . ." Illustrated Dictionary of Immunology 265 (3d ed. 2009). "FAS is a member of the TNF receptor family that is expressed on selected cells, including T cells, and renders them susceptible to apoptotic death mediated by cells expressing Fas ligand, a member of the TNF family of proteins on the cell surface." Id. Tumor necrosis factor, or TNF, are "lymphokines that are capable of causing in vivo hemorrhagic necrosis of certain tumor cells but not affecting normal cells; they have been used as experimental anticancer agents but can also induce shock when bacterial endotoxins cause their release." Tumor Necrosis Factor, Dorland's Med. Dictionary Online, https://www.dorlandsonline.com/dorland/definition?id=74613 (last visited Aug. 11, 2022).

activating keratinocytes and enhancing their expression of Fas and FasL, or by promoting the skin recruitment of lymphocytes by upregulating adhesion molecules."[44] Id.

Dr. Gershwin opined that the same mechanism thought to be involved in medication-induced hypersensitivity reactions applies to vaccines, and that "[v]accinations have been incriminated as causative agents for [SJS]/[TEN]." Pet. Ex. 11-A at 2. For support, he cited articles that described vaccine-associated SJS/TEN illnesses. The first of these, by Chahal et al.,[45] described a case report of TEN in a young woman after receipt of a meningococcal B vaccine. Pet. Ex. 11-D at 2. The patient developed "a bullous rash and painful oral lesions" eight days after vaccination. Id. at 3. The rash spread to her face, abdomen, legs, and neck. Id. "[E]rythema multiforme [("EM")] [] was favored over SJS or TEN given the targetoid nature" of her rash. Id. The rash progressed to 80% of the patient's body surface with some epidermal detachment. Id. She also had superficial erosions and crusting of her mucosal areas. Id. She developed conjunctival involvement, and "the eruption became more confluent and dusky; desquamation was observed." Id.

"The immunologic theory behind vaccine-induced cutaneous hypersensitivity" was discussed in Chahal et al. Pet. Ex. 11-D at 6. The authors stated that most "agree that antigens in the vaccine are expressed on the surface of keratinocytes, generating a CD8+ T lymphocyte immune response against epidermal cells (Type IV hypersensitivity). This leads to apoptosis of keratinocytes and detachment at the dermal-epidermal junction." Id. "The vaccine antigens are thought to be preferentially expressed in skin cells for unknown reasons, perhaps owing to individual genetic susceptibility as seen in allopurinol [] []-induced SJS/TEN" in some populations. Id.

The responsible antigen has been difficult to determine. Pet. Ex. 11-D at 6. "Several cases . . . present compelling evidence that microbial-specific proteins from the vaccines drive hypersensitivity." Id. The Chahal et al. authors cited an article by Karincaoğlu,[46] who reported EM in a child after "his first dose of diphtheria-pertussis-tetanus [("DPT")] and oral polio vaccine." Id. The vaccinations were repeated several months later, but instead of cellular pertussis, the child was given a vaccine with acellular pertussis. Id. The child did not have a reaction to the second vaccination. Id. Thus, the cellular pertussis was thought to be the offending agent. Id.

In addition to describing a case report, and discussing the causal mechanism thought to be at play, Chahal et al. also performed a literature search and identified 29 articles describing

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[44] The experts did not discuss the specific mechanism underlying this theory, as it appears they generally agree a hypersensitivity reaction occurred here. For a more thorough explanation of the relevant mechanism, see Pet. Ex. 11-C at 2-5.

[45] Dev Chahal et al., Vaccine-Induced Toxic Epidermal Necrolysis: A Case and Systematic Review, 24 Dermatology Online J. 1 (2018).

[46] Y. Karincaoğlu et al., Erythema Multiforme Due to Diphtheria-Pertussis-Tetanus Vaccine, 24 Pediatric Dermatology 334 (2007). This article was not filed in this case.

post-vaccination EM, SJS, or TEN. Pet. Ex. 11-D at 3. Of note, the authors identified allopurinol as one of "[t]he most common inciting agents of SJS/TEN." Id. at 2. By comparison, they observed that "[v]accination-induced SJS/TEN is much more rare, occurring in the published literature less than twenty times." Id. at 3.

Of the 29 articles identified by Chahal et al., three dealt with the DPT vaccine and two dealt with the diphtheria tetanus ("DT") vaccine. Pet. Ex. 11-D at 3, 7 tbl.2. The first article, authored by Leung[47] and published in 1984, reported two cases of children who developed EM after receiving DPT vaccines. Id. at 7 tbl.2. Onset was 24 hours in one child and 2 hours in the other. Id. The second article, published in 1988 by Griffith and Miller,[48] reported a case of EM in a child following DT and oral polio vaccines. Id. The third article, published in 1994 by Stratton et al.,[49] summarized a report from the Institute of Medicine, now the National Academy of Medicine. Id. It described a case of EM following the DT vaccination. Id. In an article published in 2007, by Karincaoğlu et al., discussed above, a child was reported to develop EM 10 days following DPT and oral polio vaccinations. Id. at 8 tbl.2. Lastly, a 2008 article authored by Kaur and Handa[50] reported a case of EM in a two-month-old 14 days after oral polio, DPT, hepatitis B, and flu vaccinations. Id. In all of these cases, the patients were diagnosed with EM. Id. at 7-8 tbl.2.

Chahal et al. explained that "EM, SJS, and TEN are all triggered by a delayed-type hypersensitive reaction to an offending antigen." Pet. Ex. 11-D at 4. The authors described the differences between the conditions, noting that SJS/TEN is more common "on the trunk and mucosal surfaces." Id. at 6. However, once there is "widespread involvement[,] this distinction [between EM and SJS/TEN] becomes unclear." Id. The authors concluded that "if a patient has an initial EM-like presentation that progresses to TEN, consideration for vaccination as the cause of the eruption may be paramount." Id. at 10.

Additionally, Chopra et al.[51] reported a case of EM/SJS following vaccinations for smallpox, anthrax, and tetanus. Pet. Ex. 11-I at 1. The illness was attributed to the smallpox

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[47] Alexander K.C. Leung, Erythema Multiforme Following DPT Vaccination, 77 J. Royal Soc'y Med. 1066 (1984). This article was not filed in this case.

[48] R.D. Griffith & O.F. Mille, Erythema Multiforme Following Diphtheria and Tetanus Toxoid Vaccination, 19 J. Am. Acad. Dermatology 758 (1988). This article was not filed in this case.

[49] Kathleen R. Stratton et al., Adverse Events Associated with Childhood Vaccines Other Than Pertussis and Rubella: Summary of a Report from the Institute of Medicine, 272 JAMA 1602 (1994). This article was not filed in this case.

[50] Sarvjit Kaur & Sanjeev Handa, Erythema Multiforme Following Vaccination in an Infant, 74 Indian J. Dermatology Venereology & Leprology 251 (2008). This article was not filed in this case.

[51] Ashish Chopra et al., Stevens-Johnson Syndrome After Immunization with Smallpox, Anthrax, and Tetanus Vaccines, 79 Mayo Clinic Proc. 1193 (2004).

vaccine because the patient had previously received the tetanus vaccine without incident. Id. at 4.

Dr. Gershwin cited additional papers describing case reports of EM and SJS/TEN after vaccination. Tamez et al.[52] reported a case of SJS following flu infection in a patient who received the flu vaccine three months prior to onset. Pet. Ex. 11-E at 1. Christou and Wargon[53] described a patient who developed SJS two weeks after the varicella vaccine. Pet. Ex. 11-F at 1-2. A patient who developed EM with an onset of seven days post-human papillomavirus vaccination was reported by Pérez-Carmona et al.[54] Pet. Ex. 11-G at 1. Studdiford et al.[55] described EM with onset one to two weeks after the meningitis vaccine. Pet. Ex. 11-H at 1. Dobrosavljevic et al.[56] reported a case of TEN seven days after a morbilli-parotitis-rubella vaccine. Pet. Ex. 11-J at 1. Lastly, Shoss and Rayhanazadeh[57] reported a case of TEN following measles vaccination. Pet. Ex. 11-K at 1-2.

Dr. Gershwin concluded that "any vaccine in the right genetic setting has the potential to induce a rare reaction." Pet. Ex. 25-A at 1. He illustrated this point by referencing the COVID-19 vaccination program, which has afforded scientists an opportunity to study the results of widescale immunization. Id. He noted that "there have [] been case reports of [SJS] reported from COVID-19 vaccines in which the vaccine appears to be the most likely etiologic agent."[58] Id. Dr. Gershwin concluded by opining that but for the vaccine, Ms. Mai "would not have developed [SJS]/TENS." Id. at 2.

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[52] Rebecca L. Tamez et al., Influenza B Virus Infection and Stevens-Johnson Syndrome, 35 Pediatric Dermatology e45 (2018).

[53] Elizabeth M. Christou & Orli Wargon, Stevens-Johnson Syndrome After Varicella Vaccination, 196 Med. J. Austl. 240 (2012).

[54] Lucía Pérez-Carmona et al., The Quadrivalent Human Papillomavirus Vaccine: Erythema Multiforme and Cutaneous Side Effects After Administration, 221 Dermatology 197 (2010).

[55] James Studdiford et al., Erythema Multiforme After Meningitis Vaccine: Patient Safety Concerns with Repeat Immunization, 26 Pharmacotherapy 1658 (2006).

[56] Danijela Dobrosavljevic et al., Toxic Epidermal Necrolysis Following Morbilli-Parotitis-Rubella Vaccination, 13 J. Eur. Acad. Dermatology & Venerology 59 (1999).

[57] Robert G. Shoss & Syrus Rayhanzadeh, Toxic Epidermal Necrolysis Following Measles Vaccination, 110 Archives Dermatology 766 (1974).

[58] See Pet. Ex. 25-B (Mohamed Bakir et al., Toxic Epidermal Necrolysis Post COVID-19 Vaccination – First Reported Case, 13 Cureus e17215 (2021)); Pet. Ex. 25-C (S. Dash et al., Covid-19 Vaccine Induced Steven-Johnson Syndrome: A Case Report, 46 Clinical Experimental Dermatology 1615 (2021)), Pet. Ex. 25-D (Mohamed Omar Elboraey & Emad El Said Fahim Essa, Stevens-Johnson Syndrome Post Second Dose of Pfizer COVID-19 Vaccine: A Case Report, 132 Oral Surgery Oral Med. Oral Pathology Oral Radiology E139 (2021)).

iii. Althen Prong Two

Most of Dr. Gershwin's opinions as to a logical sequence of cause and effect are discussed above in the section on his opinions as to diagnosis. Briefly, Dr. Gershwin opined that Ms. Mai had a delayed hypersensitivity reaction to her Tdap vaccine, which led to development of exfoliative dermatitis and the diagnosis of TEN. Pet. Ex. 11-A at 2-3. He believed that the condition was consistent with SJS/TEN, which has been reported following vaccinations. Id. at 2-3; Pet. Ex. 25-A at 1-2. While Dr. Gershwin agreed that SJS/TEN can be caused by allopurinol, he did not believe that occurred here, primarily because the time frame between the initial dose of allopurinol and onset of the symptoms was more than eight weeks. Pet. Ex. 11-A at 2. Additionally, he cited several case reports of SJS/TEN following vaccinations containing tetanus and diphtheria. Id.

iv. Althen Prong Three

Dr. Gershwin opined that the onset of Ms. Mai's SJS/TEN "[began] on August 15, 2015, when she developed a salmon colored blanching rash that started on her trunk and moved to her arms and legs . . . four days after receiving her Tda[p] and shingles vaccine." Pet. Ex. 11-A at 2. This places onset approximately four days after vaccination. In their article providing an overview of SJS/TEN, Borchers et al. stated that the "[m]ost suspicious [time frame] for a specific drug as the causative factor is a delay of between 4 and 28 days." Pet. Ex. 11-C at 5.

2. Respondent's Expert, Dr. Markus D. Boos[59]

a. Background and Qualifications

Dr. Boos is a board-certified dermatologist and pediatric dermatologist. Resp. Ex. A at 1; Resp. Ex. B at 2. After receiving his Ph.D. in immunology and his M.D. from the University of Chicago, he completed a pediatric internship, dermatology residency, and a pediatric dermatology fellowship. Resp. Ex. B at 1. Since 2015, he has worked at Seattle Children's Hospital and as an assistant professor at the University of Washington, and he has run a Dermatology-Immunology Clinic. Id.; Resp. Ex. A at 1. "In [his] current practice, [he is] frequently involved in identifying and treating drug hypersensitivity reaction as well as their mimics," and has "treated approximately 20-25 patients with diagnosed SJS/TEN (and countless others in whom this diagnosis was considered) and hundreds of other patients with adverse cutaneous drug eruptions." Resp. Ex. A at 1. Additionally, Dr. Boos has authored or co-authored over 46 publications. Resp. Ex. B at 7-11.

[59] Dr. Boos provided three expert reports. Resp. Exs. A, H, I.

b. Opinion

i. Diagnosis

Dr. Boos opined that Ms. Mai did not have SJS/TEN or a TEN-like illness but instead had DRESS syndrome, "also known as drug hypersensitivity syndrome (DHS)."[60] Resp. Ex. A at 6. He explained that "DRESS[] is a severe drug hypersensitivity reaction most often precipitated by anticonvulsant and antimicrobial medications, though other medications, most notably allopurinol, are also known to frequently induce the reaction." Id. As compared with other drug reactions, DRESS usually presents within two months of initial exposure to the offending medication, which is more prolonged than other types of cutaneous hypersensitivity reactions. Id.

In addition to the prolonged latency period between exposure and onset of illness, the differences between DRESS and SJS/TEN include the appearance of the rash, involvement of mucous membranes, and pain. Resp. Ex. A at 6. Dr. Boos opined that SJS/TEN is "characterized by blisters/epidermal detachment" and "is usually associated with skin pain." Id. (citing Resp. Ex. A, Tab 1 at 4).[61] Dr. Boos agreed with Dr. Gershwin that the "skin lesions are flat, irregular, atypical target lesions or diffuse purpuric macules that frequently have necrotic centers." Id. "[T]he epidermis detaches from the dermis, giving rise to flaccid blisters. In TEN, loss of epidermis is often sheet-like, with . . . lateral displacement of the necrotic epidermis in response to slight pressure." Id. (emphasis omitted) (quoting Pet. Ex. 11-C at 5). In the majority of patients (90%), mucous membranes are involved. Id. (citing Pet. Ex. 11-C at 5). Painful erosions can occur on the ocular (eye) mucosa. Id. (citing Pet. Ex. 11-C at 5).

Dr. Boos stated that when Ms. Mai was first admitted, she had "[n]o target lesions or mucosal involvement." Resp. Ex. A at 6 (quoting Pet. Ex. 7 at 68). Further, she did not have "any lesions of oral mucosa or desquamation that would be typical for [SJS]." Id. (quoting Pet. Ex. 7 at 69). Dr. Boos emphasized, in a supplemental report, that Ms. Mai did not have areas of desquamation, no vesicles or scales, and no oral or tongue lesions.[62] Resp. Ex. H at 2. According to Dr. Boos, Ms. Mai's rash was not consistent with SJS/TEN. Resp. Ex. A at 8. Instead, it had "multiple features" consistent with a rash seen in DRESS syndrome, "including a

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[60] DRESS is also referred to as "drug-induced hypersensitivity syndrome (DiHS) by Japanese experts." Resp. Ex. A, Tab 2 at 1 (Yung-Tsu Cho et al., Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS): An Interplay Among Drugs, Viruses, and Immune System, 18 Int'l J. Molecular Scis. 1 (2017)).

[61] Michael R. Ardern-Jones & Maja Mockenhaupt, Making a Diagnosis in Severe Cutaneous Drug Hypersensitivity Reactions, 19 Current Op. Allergy & Clinical Immunology 283 (2019).

[62] "[S]evere oral mucositis is a very rare clinical finding in patients with DRESS syndrome. . . . Severe mucositis . . . is more indicative of DRESS/[SJS] overlap, which is a very rare clinical entity." Resp. Ex. A, Tab 6 at 1 (Misha Rosenbach et al., Drug Reaction with Eosinophilia and Systemic Symptoms Syndrome: A Picture Is Worth a Thousand Words, 69 J. Am. Acad. Dermatology 1056 (2013)).

pruritic, widespread, macular rash, relative sparing of the mucosal surfaces throughout much of her clinical course, early involvement of the face[,] and eventual evolution to a persistent exfoliative dermatitis." Id.

He also noted that Ms. Mai had "persistent dysphagia and had [] involvement of the liver and kidneys," which are common features in DRESS syndrome. Resp. Ex. A at 6-8.

Additionally, according to Dr. Boos, a patient with SJS/TEN would require a more prolonged hospital stay for supportive treatment, usually two to six weeks in duration, depending on the amount of skin involved. Resp. Ex. A at 6. He opined that "[t]he fact that [Ms. Mai] was discharged 4 days after admission [] argues against a diagnosis of SJS or TEN." Id.

By comparison, Dr. Boos, citing Husain et al., opined that DRESS "is characterized by prodromal symptoms of itch and fever" preceding a rash that is diffuse, itchy, macular, and usually "begins on the face, upper trunk, and extremities," but becoming generalized, and "at times developing into an exfoliative dermatitis." Resp. Ex. A at 6 (citing Resp. Ex. A, Tab 5 at 5). While mucosal involvement "is possible," it is "less pronounced that in SJS/TEN." Id. (citing Resp. Ex. A, Tab 5 at 5). Facial edema, including around the eyes, and dysphagia may also be present. Id. (citing Resp. Ex. A, Tab 3 at 1-2).[63] "The cutaneous eruption of DRESS[] is noted to become darker with time, and may remain persistent for months after discontinuing the inciting agent." Id. at 6-7 (citing Resp. Ex. A, Tab 5 at 5). Additionally, there may be organ involvement, including liver disease and elevated liver function tests. Id. at 7 (citing Resp. Ex. A, Tab 5 at 5-7). Dr. Boos stated that kidney injury is often seen when the illness is caused by allopurinol. Id. (citing Resp. Ex. A, Tab 5 at 7). Although most patients recover from DRESS, mortality is 10%, often due to septic shock with multi-organ failure, and "prognosis is particularly guarded for the elderly." Id. (citing Resp. Ex. A, Tab 4 at 8).

Regarding histological findings, Dr. Boos asserted that Ms. Mai's biopsy "[was] very similar" to what is seen in DRESS, which Husain et al. described as "a dense, perivascular lymphocytic infiltrate in the papillary dermis, with . . . extravasated erythrocytes, eosinophils, and dermal edema." Resp. Ex. A at 7 (quoting Resp. Ex. A, Tab 5 at 8-9). Ms. Mai's biopsy showed, in part, "a dense perivascular lymphohistiocytic infiltrate intermixed with a few eosinophils with mild exocytosis into epidermis." Id. (quoting Pet. Ex. 7 at 71). Additionally, he opined that "Ms. Mai's biopsy results [were] inconsistent with a diagnosis of SJS/TEN."[64] Resp. Ex. H at 2.

Further, even though a formal assessment tool to diagnose DRESS syndrome was not used to diagnose Ms. Mai's rash, Dr. Boos opined that the RegiSCAR scoring system can be

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[63] Vincent Descamps, Dysphagia, a Major Early Manifestation in DRESS Syndrome, 69 J. Am. Acad. Dermatology 1057 (2013).

[64] For more detail about the histopathological basis of Dr. Boos' opinion about Ms. Mai's biopsy, see Resp. Ex. H at 1-3; Resp. Ex. H, Tab 1 at 328-30 (1 Jean L. Bolognia et al., Dermatology (Jeffrey P. Callen et al. eds., 3d ed. 2012)).

used retrospectively to diagnose DRESS syndrome. Resp. Ex. A at 8. The RegiSCAR criteria are set forth below:

Table 2. The RegiSCAR scoring system for diagnosing DRESS syndrome.

Items	Score			Comments
	−1	0	1	
Fever ≧ 38.5 °C	N/U	Y		
Enlarged lymph nodes		N/U	Y	>1 cm and ≧ 2 different areas
Eosinophilia ≧ 0.7×10^9/L or ≧ 10% if WBC < 4.0×10^9/L		N/U	Y	Score 2, when ≧ 1.5×10^9/L or ≧ 20% if WBC < 4.0×10^9/L
Atypical lymphocytosis		N/U	Y	
Skin rash Extent > 50% of BSA Rash suggesting DRESS	 N	 N/U U	 Y Y	Rash suggesting DRESS: ≧ 2 symptoms: purpuric lesions (other than legs), infiltration, facial edema, psoriasiform desquamation
Skin biopsy suggesting DRESS	N	Y/U		
Organ involvement		N	Y	Score 1 for each organ involvement, maximal score: 2
Rash resolution ≧ 15 days	N/U	Y		
Excluding other causes		N/U	Y	Score 1 if 3 tests of the following tests were performed and all were negative: HAV, HBV, HCV, Mycoplasma, Chlamydia, ANA, blood culture

ANA: anti-nuclear antibody; BSA: body surface area; HAV: hepatitis A virus; HBV: hepatitis B virus; HCV: hepatitis C virus; N: no; U: unknown; WBC: white blood cell; Y: yes.

Resp. Ex. A, Tab 2 at 6 tbl.2. Cho et al. noted a DRESS syndrome diagnosis is made based on the total score. Id. at 6. A score of two to three points is a "possible" case of DRESS, a score of four to five points is a "probable case" of DRESS, and a score of more than five points is a "definite case" of DRESS. Id.

Dr. Boos opined that based on the medical record documentation obtained during Ms. Mai's first hospital admission, she had a score of five or greater, which he labeled as "probable or definitive DRESS." Resp. Ex. A at 8. This score was based on an elevated white blood cell count of 21.6 with 28% eosinophils (two points), a rash greater than 50% of her body surface area (one point), liver and kidney involvement (two points), and the fact that a workup excluded alternative causes (one point). Id. at 8-9.

In his second expert report, Dr. Boos summarized the reasons for his opinion that Ms. Mai did not have SJS/TEN:

SJS/TEN	**Ms. Mai's Presentation**
Clinical ▪ symmetrical spread of rash from the face and trunk to the extremities ▪ erythema, dusky or violaceous macules ▪ gray hue	Clinical ▪ rash on trunk and extremities, sparing the palms and soles ▪ confluent, blanching ▪ salmon hue ▪ no areas of desquamation, no blisters or skin sloughing

▪ bullae, epidermal sloughing, frank skin necrosis ▪ morbilliform or atypical targetoid lesions ▪ painful oral, ocular, and/or genital mucositis with mucosal erosions ▪ Nikolsky sign: separation of papillary dermis from basal layer upon gentle lateral pressure ▪ Asboe-Hansen sign: lateral extension of bullae with pressure	▪ no target lesions ▪ no reported involvement of mouth, eyes, or genitalia ▪ no mention of Nikolsky sign ▪ no mention of Asboe-Hansen sign
Histological ▪ apoptotic keratinocytes scattered in basal and immediate suprabasal epidermis (dead skin cells at base of epidermis) ▪ subepidermal blister with overlying confluent necrosis of entire epidermis ▪ sparse perivascular infiltrate composed primarily of lymphocytes	Histological ▪ hyperkeratosis (increased number of skin cells in epidermis) ▪ focal parakeratosis (some skin cells retain nuclei in stratum corneum of epidermis) ▪ spongiosis (intercellular edema of epidermis without blistering) ▪ focal vacuolar interface changes (nonspecific space formed around select cells at base of epidermis; no blistering) ▪ dense perivascular lymphohistiocytic infiltrate (infiltrate composed of lymphocytes and histiocytes)

Resp. Ex. H at 3.

He also reviewed Ms. Mai's medical records and concluded that she was never diagnosed with SJS/TEN by a dermatologist. Resp. Ex. H at 3-6. There was a reference to TEN after her first hospitalization, when she was first seen by a dermatologist, Dr. Luu. Id. at 4. Dr. Luu described Ms. Mai's condition as a "TEN-like reaction with widespread scaling erythroderma," and he diagnosed her with an "adverse drug reaction." Id. at 4-5 (quoting Pet. Ex. 6 at 11). Dr. Luu advised Ms. Mai to follow up as needed. Id. at 5. Dr. Boos stated that this reaction by Dr. Luu "would be highly atypical if a doctor actually believed that a patient had TEN, which evolves quickly . . . and is associated with significant mortality." Id. (emphasis omitted).

A "TEN-like reaction" is a phrase that, according to Dr. Boos, is commonly used to describe lupus erythematosus "characterized by prominent bullae that is reminiscent of TEN." Resp. Ex. H at 5. He emphasized that the condition "is not precipitated by medication." Id. (emphasis omitted). The expression, "TEN-like," may also be used to describe other conditions that are not related to adverse drug reactions. Id. Dr. Boos suggested that Dr. Luu was "imprecisely using" the phrase "to denote persistent erythroderma with skin flaking in a patient that had been previously hospitalized for an adverse drug reaction with systemic aberrations."

Id. For this and other reasons described in his expert report, Dr. Boos believed that "Dr. Luu's use of the term 'TEN-like' [was] as a description rather than a diagnosis." Id.

Further, Dr. Boos noted that when Ms. Mai was admitted to the hospital in December 2015, a physician in the ED had a telephone consultation with a dermatologist at another hospital who reviewed photographs of Ms. Mai. Resp. Ex. H at 4. That consultation was documented as, "[discussed with] dermatologist at VMC who reviewed photos of the patient's rash and states it is not consistent with [SJS] and believes it to be exfoliative dermatitis." Id. (quoting Pet. Ex. 19 at 28).

In his third expert report, Dr. Boos offered his opinions as to the recently filed photographs and accompanying affidavit. Resp. Ex. I at 1 (citing Pet. Exs. 24-25). Dr. Boos opined that the photographs of "Ms. Mai's cutaneous and systemic findings . . . [were] classic for DRESS." Id. at 3. He explained that

> [f]rom 9/3/15 to 9/7/15, Ms. Mai was admitted to San Jose Regional Medical Center . . . . Exhibits 24B & 24C, photos from 9/17/15 and 9/19/15, provide further insight into the nature of Ms. Mai's eruption in mid-September, after treatment with steroids and discharge from the hospital, but before she visited with dermatologist Dr. Michael Luu on 9/29/15. Exhibit 24B shows an extensive exfoliative dermatitis of the skin of the hands and shoulder with moderate background erythema (redness). Exhibit 24C shows similar evidence of an intense, more violaceous or dusky background erythema and desquamation of the face and adherent scale-crust of the neck. (See Exhibit 24A for comparison of Ms. Mai's skin redness (absent) and quality (no scale apparent) prior to onset of her drug eruption). Most importantly, however, is the striking mid-facial swelling in Exhibit 24C that is especially notable when compared to Exhibit 24A, prior to the onset of Ms. Mai's eruption. Taken together, the evolution of Ms. Mai's rash is a textbook description of DRESS syndrome . . . .

Id.

ii. Althen Prong One

Dr. Boos did not offer an opinion rebutting Dr. Gershwin's proffered mechanistic theory of drug hypersensitivity reaction. He did, however, state that "[he] [did] not find any evidence in the medical literature of DRESS[] caused by the Tdap vaccine." Resp. Ex. A at 8. While he acknowledged the cases reports that associate vaccination with SJS/TEN, he stated that "it is important to recognize that case reports do not establish causation." Resp. Ex. H at 10. He also cautioned that case reports "are [] frequently confounded by concomitant use of medications." Id.

In support of his opinions, Dr. Boos cited several articles that failed to find evidence to support vaccine-related SCARs. Grazina et al.[65] performed a systematic review of scientific databases regarding vaccines, including tetanus and diphtheria, tetanus, acellular pertussis and inactivated poliovirus ("DTaP-IPV"), and concluded that "[n]one of the [] studies reported statistically significant associations between vaccination and [SJS]. . . . Regarding the case reports, there was not sufficient evidence to form a positive association." Resp. Ex. H, Tab 3 at 1.

Dr. Boos also cited a study authored by Su et al.[66] that examined data from the Vaccine Adverse Event Reporting System ("VAERS") from 1999 to 2017 on EM, SJS, and TEN after vaccinations. Resp. Ex. H, Tab 17 at 1. During that time frame, there were 984 cases of EM, 89 cases of SJS, six cases of SJS/TEN, and seven cases of TEN. Id. DTaP vaccination was administered in 18% (199 cases) of the cases, and in only 17 cases was DTaP administered alone. Id. at 3, 4 tbl.3. The authors "identified no notable vaccine-[adverse event] combinations for EM/SJS/TEN following vaccination overall." Id. at 5. Their "data suggest[ed] that EM/SJS/TEN is reported no more frequently after vaccination than after known causes of these conditions," and they concluded that "EM/SJS/TEN rarely occur after vaccination." Id. at 5-6.

He also criticized the Solak case report, cited by Dr. Gershwin, discussing a patient with DRESS secondary to allopurinol, where the authors suggested that a flu vaccine one week before symptom onset may have played a causal role. Resp. Ex. H at 11 (citing Pet. Ex. 13-C at 1). Dr. Boos found that the authors' conclusion that the flu vaccine may have played a role in disease onset was speculative since they offered no supportive evidence. Id. Similarly, Dr. Boos was critical of another case report from Griffin et al.[67] that described a temporal association between the flu vaccine and the onset of DRESS. Id. (citing Resp. Ex. H, Tab 4 at 1). There, the patient was also taking the medication sitagliptin,[68] which Dr. Boos explained has been linked with DRESS. Id. (citing Resp. Ex. H, Tab 4 at 1; Resp. Ex. H, Tab 15 at 2 (noting a link between sitagliptin and DRESS)).[69]

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[65] I. Grazina et al., Is There an Association Between Stevens-Johnson Syndrome and Vaccination? A Systematic Review, 32 Annali Igiene 81 (2020).

[66] John R. Su et al., Erythema Multiforme, Stevens Johnson Syndrome, and Toxic Epidermal Necrolysis Reported After Vaccination, 1999-2017, 38 Vaccine 1746 (2020).

[67] David W.J. Griffin et al., A Case of Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) Without a Typical Precipitant, 212 Med. J. Austl. 300 (2020).

[68] Sitagliptin is used in the treatment of type II diabetes mellitus. Sitagliptin Phosphate, Dorland's Med. Dictionary Online, https://www.dorlandsonline.com/dorland/definition?id=45968 (last visited Aug. 11, 2022). A trademark for sitagliptin is Januvia, which Ms. Mai was prescribed. Januvia, Dorland's Med. Dictionary Online, https://www.dorlandsonline.com/dorland/definition?id=26537 (last visited Aug. 11, 2022); Pet. Ex. 7 at 7; Pet. Ex. 19 at 944.

[69] C. Sin et al., Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) in a Patient Taking Sitagliptin, 38 Diabetes & Metabolism 571 (2012).

iii. Althen Prong Two

The majority of Dr. Boos' focus in his expert reports relate to his opinion that, more likely than not, Ms. Mai had DRESS, which he believed was caused by allopurinol. Resp. Ex. A at 10. He disagreed that the Tdap vaccination was the offending medication, and opined that "there [was] a paucity of clinical or laboratory evaluation" to support either the diagnoses of SJS/TEN or causative association with the Tdap vaccine. Id.; see also Resp. Ex. H at 10-13. He stated that the Tdap vaccine "is not recognized as a common cause of drug hypersensitivity reactions in the dermatologic community, particularly if there is documented exposure to a more common culprit medication." Resp. Ex. A at 8. Dr. Boos concluded that the Tdap vaccine did not play "any role in [Ms. Mai's] condition or demise." Id. at 10.

Dr. Boos opined that Ms. Mai's clinical course was not consistent with SJS/TEN, and he presented a number of reasons why he believed that Ms. Mai's clinical course and skin eruption was consistent with allopurinol-triggered DRESS syndrome. Resp. Ex. A at 6-10; Resp. Ex. H at 1-10; Resp. Ex. I at 3-5. Most of his opinions in this regard were presented above, in the section on diagnosis.

Additionally, Dr. Boos opined that Ms. Mai had a "waxing and waning course following her initial presentation," which he attributed to two factors: (1) failure to discontinue allopurinol, "the culprit medication" and (2) "suboptimal[] treat[ment] with corticosteroids." Resp. Ex. A at 9.

Based on his review of the medical records, Dr. Boos explained that the documentation of the "timeline of [Ms. Mail's] medications" was "spotty at best." Resp. Ex. A at 9. "Arguing in favor that she was continually on allopurinol" is the decrease in her uric acid level from 8.3 on May 23, 2015 (prior to initiation of treatment) to 4.9 on August 29, 2015. Id. However, when Ms. Mai was admitted to the hospital on September 3, 2015, Dr. Boos noted that "[i]t does not appear that anyone mentioned that Ms. Mai had begun taking allopurinol." Resp. Ex. H at 8. He further noted that "the admitting physician, Dr. Sanghavi, initially considered DRESS as Ms. Mai's diagnosis, but then dismissed it because she thought that Ms. Mai 'ha[d] not had any introduction of new medications within the last 2 to 6 weeks.'"[70] Id. (quoting Pet. Ex. 7 at 67).

Moving forward, Dr. Boos noted that allopurinol was listed as a current medication on October 16, 2015, when Ms. Mai was seen by a gastroenterologist. Resp. Ex. A at 9 (citing Pet. Ex. 4 at 6). Allopurinol was again listed as a current medication when she returned for a follow-up visit on October 30, 2015. Id. (citing Pet. Ex. 4 at 4). When Ms. Mai returned to the hospital on December 19, the records indicated that the family did not bring her medication list and allopurinol was not listed as one of her current medications. Id. (citing Pet. Ex. 7 at 7). Dr. Boos surmised that the omission in the hospital records of allopurinol as a current medication "may have led to [Ms. Mai's] myriad providers missing the diagnosis of DRESS[]." Id.

[70] Dr. Boos also noted that "the window for DRESS is typically considered up to 2 months, though in [his] experience it can be longer and a time of onset beyond 2 months would not necessarily preclude the diagnosis." Resp. Ex. H at 8.

According to Dr. Boos, the pharmacy records show that Ms. Mai obtained her initial prescription of a 90-day supply of allopurinol on June 18, 2015, that Ms. Mai possibly refilled the prescription on September 2, 2015, and that Ms. Mai refilled the prescription on November 23, 2015, obtaining a 30-day supply. Resp. Ex. H at 8-9 (citing Pet. Ex. 23 at 3-6). Based on this evidence, and the identification of allopurinol in the gastroenterology records on October 16 and 30, 2015, Dr. Boos opined that while the records are "not entirely clear, there is evidence throughout Ms. Mai's medical record that she continued to take allopurinol from sometime on or perhaps shortly after [June 18, 2015] until the time of her death."[71] Id. at 9.

Regarding Dr. Boos' opinion that Ms. Mai received "suboptimal[] treat[ment] with corticosteroids," he first noted that she "responded to systemic corticosteroid therapy" during her first hospital admission, "consistent with a diagnosis of DRESS[]." Resp. Ex. A at 9. He explained that her laboratory values improved, and by October 8, 2015, her rash was "completely resolved." Id. On October 16, 2015, her liver function tests were also improved. Id. She was noted to be on oral prednisone at that time. Id. When Ms. Mai saw Dr. Nguyen on November 23, 2015, he noted that her rash was better, and he decreased her prednisone dose. Id. At the next visit on December 14, 2015, however, Ms. Mai complained of "itchy rash all over." Id. Dr. Nguyen documented that she had elevated liver function studies, although he did not document the actual results. Id. Dr. Boos opined that "these findings indicate that this dose of prednisone was subtherapeutic and caused relapse of her DRESS[]." Id.

Dr. Boos opined that Ms. Mai improved once she was given high doses of steroids during her second hospital admission, but then her condition deteriorated. Resp. Ex. A at 9. He opined that her cause of death, which included circulatory shock, kidney and liver dysfunction, coagulopathy, and gastrointestinal bleeding, "increased her risk of death from her improperly diagnosed and treated condition." Id. (citing Resp. Ex. A, Tab 4 at 8). Dr. Boos concluded that "[g]iven that the most important measure in treating DRESS is early recognition . . . and immediate withdrawal of the suspected drug, her worsening clinical course, inadequately relieved only by intermittent bursts of systemic steroids, is appropriately explained by persistent exposure to allopurinol triggering her multiorgan system hypersensitivity reaction," which "eventually lead to system dysfunction and ultimately death." Resp. Ex. H at 9-10 (internal citations and quotes omitted).

[71] Dr. Boos' conclusion is not entirely accurate. The medication administration records for Ms. Mai's two hospitalizations (September 3-7, 2015, and December 19, 2015 through her death on January 2, 2016) do not indicate that allopurinol was administered to her during either hospital stay. Pet. Ex. 19 at 388-437, 439-63, 944, 1112. The undersigned also disagrees that the pharmacy records indicate a refill of allopurinol was obtained on September 2, 2015. See Pet. Ex. 23 at 3. Regardless of these possible inaccuracies, the undersigned agrees with Dr. Boos that the evidence does show that Ms. Mai was taking allopurinol on October 16 and 30, 2015, and that she obtained a refill on November 23, 2015, evidencing that she had, by that time, taken 90 tablets. The fact that she obtained the refill of 30 pills on November 23, 2015, also suggests that she continued to take allopurinol, at least as long was she was able to do so (depending on whether she was able to take medication due to her mouth lesions and overall poor condition), or until she was hospitalized on December 19, 2015.

In his second expert report, Dr. Boos discussed two additional concepts relevant to his opinions. The first was "the probable role of anchoring bias" that "[gave] rise to the notion that Ms. Mai's condition was caused by a vaccine." Resp. Ex. H at 11. He defined "anchoring" in the medical context, as "decision-making behavior in which a 'single piece of information strongly influences a decision, particularly data encountered early in a given situation.'" Id. (quoting Resp. Ex. H, Tab 11 at 2).[72] Dr. Boos explained that this type of bias can "result in a diagnosis being accepted without considering other possible explanations for an individual's presentation." Id. In the context of this case, Dr. Boos stated that Ms. Mai received her vaccination on August 11, 2015, and when she presented to the ED on September 3, 2015, she reported that she had recently had a vaccination, although she reported the wrong date, and that she had developed a rash several days later. Id. at 11-12. From this point forward, the record "suggest[s] that, because Ms. Mai's vaccination was initially reported as the triggering event—with no mention of allopurinol use and no discussion of possible earlier onset of symptoms—the connection between her skin condition and her vaccination was then presumed without further investigation or evaluation by subsequent providers." Id. at 12. Dr. Boos also explained that the same anchoring bias may have attached to the phrase "TEN-like reaction" used by Dr. Luu to describe Ms. Mai's condition. Id.

The second concept was related to the inferences and opinions in his expert reports suggesting that physicians missed the diagnosis of DRESS triggered by allopurinol, and that by doing so, they committed malpractice.[73] Resp. Ex. H at 12. Dr. Boos provided a frame of reference by explaining that DRESS is rare and that the study of drug reactions is not usually taught in medical school. Id. While dermatologists are trained in the diagnosis and treatment of skin eruptions, primary care physicians and other specialists are not. Id. Thus, Dr. Boos would not expect them to make a diagnosis of DRESS, even with input of a dermatologist who lacks complete information. Id. Dr. Boos further explained that "[t]hese kinds of gaps in information are, unfortunately, a very well-documented phenomenon in medicine, and they do not necessarily mean that any particular provider was negligent." Id.

Specifically as to Ms. Mai, Dr. Boos opined that her "case was complex." Resp. Ex. H at 12. She had a significant medical history for which she took many medications. Id. In 2015,

> she saw providers of different specialties, [] was admitted to the hospital twice, and it does not appear that the entirety of her clinical history, including diagnosis and medications, was available to all the treating physicians. Her misdiagnosis appears to be largely secondary to problems with communication and coordination of vital healthcare information amongst family and providers, between providers, and between the inpatient and outpatient settings. Fundamental to Ms. Mai's misdiagnosis is that, at the time of her first hospital on

[72] Megan Richie & S. Andrew Josephson, Quantifying Heuristic Bias: Anchoring, Availability, and Representativeness, 30 Teaching & Learning Med. 67 (2018).

[73] To the extent the experts discussed whether Ms. Mai's treating physicians missed the diagnosis of a drug reaction caused by allopurinol, that issue need not be addressed by the undersigned as it is not relevant to the issue of causation herein.

> [September 3, 2015], allopurinol does not appear to have been provided to her healthcare team as a medication that she had been using. As such, when concern for DRESS was raised, it was summarily dismissed because they thought she had not had any recent introduction of new medications. This diagnosis does not appear to have been reconsidered as Ms. Mai improved with systemic steroids (first line treatment for DRESS); she was therefore given a nonspecific diagnosis of "severe dermatitis" at the time of discharge.

Id. at 12-13 (internal citations omitted). Dr. Boos concluded that "[n]ot recognizing a diagnosis of DRESS . . . [was] not the fault of any one provider, but a systems-based problem where individuals knowledgeable about the diagnosis of DRESS did not have access to all of the relevant information needed to make the diagnosis." Id. at 13.

iv. Althen Prong Three

Dr. Boos opined that Ms. Mai's initial symptoms of DRESS occurred between August 6, 2015, "when she first reported an itchy macular rash to her face," and August 27, 2015, "when she re-presented with fevers, fatigue[,] and a macular rash."[74] Resp. Ex. A at 8. Although Ms. Mai's physician, Dr. Nguyen, opined that Ms. Mai's rash on June 16 and August 6 was different than her post-vaccination rash, Dr. Boos did not find this opinion reliable because Dr. Nguyen's documentation of the rash on these visits was the same: "nontender, macular rash." Id. Further, in spite of the fact that Dr. Nguyen described the rash in the same manner at each of these visits, "Dr. Nguyen alternately diagnosed [Ms. Mai] with urticaria, dermatitis[,] or an allergic reaction." Id. According to Dr. Boos, these factors "call[] into question the reliability of his assessment." Id.; see also Resp. Ex. H at 9.

Based on the records, Dr. Boos observed that Ms. Mai was prescribed allopurinol 300 mg once daily on June 18, 2015, two months before her initial symptoms. Resp. Ex. A at 8. He concluded that her Tdap vaccination, administered on August 11, 2015, occurred after the first symptoms of DRESS. Id. Dr. Boos cited Husain et al. in support of his opinion that "DRESS[] typically presents within 2 months of first exposure to the inciting agent, which is longer than other cutaneous drug hypersensitivities." Id. at 6 (citing Resp. Ex. A, Tab 5 at 2). Even assuming that Ms. Mai's rash began four days after vaccination, on approximately August 15, 2015, Dr. Boos asserted that her "symptoms would have begun approximately 8 weeks and 2 days after she started taking allopurinol, which is consistent with the typical 2-month onset window expected for DRESS." Resp. Ex. H at 9 (emphasis omitted).

[74] Dr. Boos also stated that Ms. Mai's DRESS began "sometime between late June to mid-August 2015, within two months of initiating treatment with allopurinol." Resp. Ex. H at 8.

3. Respondent's Expert, Dr. You-Wen He[75]

a. Background and Qualifications

Dr. He is an immunology professor at Duke University Medical Center. Resp. Ex. C at 1; Resp. Ex. D at 1. Since obtaining his M.D. in China in 1986, he received an M.S. from the Institute of Microbiology and Epidemiology in Beijing in 1989 and a Ph.D. from the Department of Microbiology & Immunology from the University of Miami School of Medicine in 1996. Resp. Ex. D at 1. He serves as an editor or member for several biomedical journals and has authored or co-authored over 100 publications. Resp. Ex. C at 1-2; Resp. Ex. D at 2-3, 9-17.

b. Opinion

The majority of Dr. He's expert report addressed Dr. Gershwin's opinions, as they relate to the diagnosis of SJS/TEN. Resp. Ex. C at 3. Dr. He opined that "the vaccines [Ms. Mai] received had no role in her skin reaction." Id.

i. Diagnosis

Dr. He deferred to Dr. Gershwin and Dr. Boos as to the issue of diagnosis. Resp. Ex. C at 3.

ii. Althen Prong One

Dr. He did not offer any opinion rebutting Dr. Gershwin's opinion that SJS/TEN are hypersensitivity reactions. He agreed that the conditions are "due to severe cutaneous inflammation and delayed hypersensitivity reaction." Resp. Ex. C at 2. He also agreed that the cause of the conditions include drugs or medications, which account for the majority of cases (50-80%). Id. He stated that "allopurinol is consistently ranked as one of the top causative factors." Id.

Dr. He cited a number of articles supporting his position that allopurinol is a known cause of SJS/TEN and fatal hypersensitivity reactions. Yang et al.[76] reported the results of a nationwide study done in Taiwan based on data obtained from a national database of medical records of 23 million patients. Resp. Ex. C, Tab 3 at 1. They reviewed data from 2005 to 2011 and identified 495,863 patients who had been newly prescribed allopurinol. Id. at 1, 3. Of these, "the annual incidence rates were 4.68 per 1000 new users for allopurinol hypersensitivity, 2.02 per 1000 new users for related hospitalization, and 0.39 per 1000 new users for related mortality." Id.

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[75] Respondent filed one expert report from Dr. He. Resp. Ex. C.

[76] Chien-Yi Yang et al., Allopurinol Use and Risk of Fatal Hypersensitivity Reactions: A Nationwide Population-Based Study in Taiwan, 175 JAMA Internal Med. 1550 (2015).

The second study cited by Dr. He was by Kang et al.,[77] who analyzed data from the Korea Adverse Event Reporting System from 1988 to 2013. Resp. Ex. C, Tab 4 at 1. The authors found 755 SCAR cases, and of these, 508 were SJS/TEN, and 247 were DRESS. Id. "Allopurinol was the most common causative drug." Id.

In another study, authored by Nguyen et al.,[78] the authors examined data from the Vietnamese database for adverse drug reactions from 2010 to 2015, and identified 2,849 reports of medium- and late-onset SCARs. Resp. Ex. C, Tab 5 at 1. Of these, 136 patients were diagnosed with SJS/TEN. Id. Allopurinol was the third most reported causal medication associated with SJS/TEN. Id. at 5.

In addition, Dr. He cited articles from a number of other countries, including the United States, United Kingdom, Israel, Thailand, Spain, Italy, and China, all identifying allopurinol as a "common causative factor in SJS/TEN patients." Resp. Ex. C at 3 (citing Resp. Ex. C, Tab 6;[79] Resp. Ex. C, Tab 7;[80] Resp. Ex. C, Tab 8;[81] Resp. Ex. C, Tab 9;[82] Resp. Ex. C, Tab 10;[83] Resp.

[77] Min-Gyu Kang et al., Analysis of Individual Case Safety Reports of Severe Cutaneous Adverse Reactions in Korea, 60 Yonsei Med. J. 208 (2019).

[78] Khac-Dung Nguyen et al., Drug-Induced Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis in Vietnamese Spontaneous Adverse Drug Reaction Database: A Subgroup Approach to Disproportionality Analysis, 44 J. Clinical Pharmacy & Therapeutics 69 (2019).

[79] Na Lu et al., Racial Disparities in the Risk of Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis as Urate-Lowering Drug Adverse Events in the United States, 46 Seminars Arthritis & Rheumatism 253 (2016).

[80] Noel Frey et al., The Epidemiology of Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis in the UK, 137 J. Investigative Dermatology 1240 (2017).

[81] Nicola Maggio et al., Causative Drugs of Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis in Israel, 57 J. Clinical Pharmacology 823 (2017).

[82] Panita Limpawattana et al., Clinical Profiles of Stevens-Johnson Syndrome Among Thai Patients, 41 J. Dermatology 634 (2014).

[83] Sara Rodríguez-Martín et al., Incidence of Stevens-Johnson Syndrome/Toxic Epidermal Necrolysis Among New Users of Different Individual Drugs in a European Population: A Case-Population Study, 75 Eur. J. Clinical Pharmacology 237 (2019).

Ex. C, Tab 11;[84] Resp. Ex. C, Tab 12).[85] In the Thai study, "[a]llopurinol had the strongest association with SJS in older patients as compared to the younger ones." Resp. Ex. C, Tab 9 at 1. Further, Lu et al. observed that there is an "overrepresentation of Asians" who suffer allopurinol hypersensitivity syndromes. Resp. Ex. C, Tab 6 at 1, 3.

In contrast, Dr. He noted that "a PUBMED search[86] did not find any report on Tdap vaccine and SJS/TEN." Resp. Ex. C at 3. Although Dr. Gershwin referred to a case report of a tetanus vaccine associated with SJS, Dr. He explained that the patient in the report received several vaccines, and the illness was thought to be caused by smallpox vaccination, not tetanus, since the patient had previously received the tetanus vaccine without incident. Id. (citing Pet. Ex. 11-I at 1).

Dr. He concluded that "there is not a single case report on SJS/TEN that is caused by Tdap. Millions of people have received this vaccine. The lack of case report on Tdap vaccine and SJS/TEN indicates that this vaccine is highly unlikely the cause of this disease." Resp. Ex. C at 3.

iii. Althen Prong Two

Dr. He opined that "there is no reliable evidence to support [Dr. Gershwin's] theory that the vaccines caused or contributed to Ms. Mai's SJS/TEN." Resp. Ex. C at 4. Instead, he believed that "Ms. Mai's SJS/TEN was caused by the allopurinol she took on June 18, 2015." Id.

He explained that risk factors for allopurinol hypersensitivity include being female, being 60 years of age or older, taking an initial allopurinol dose of more than 100 mg per day,[87] having comorbidities including kidney and heart disease, and using allopurinol for treatment of asymptomatic elevated uric acid levels (hyperuricemia). Resp. Ex. C at 3. For support, Dr. He cited the Yang et al. nationwide population-based study in Taiwan, where the authors identified risk factors for allopurinol hypersensitivity, which "included female sex, age 60 years or older, initial allopurinol dosage exceeding 100 mg/d, renal or cardiovascular comorbidities, and use for treating asymptomatic hyperuricemia." Resp. Ex. C, Tab 3 at 1. The authors found that the

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[84] Janouk Diphoorn et al., Incidence, Causative Factors and Mortality Rates of Stevens-Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN) in Northern Italy: Data from the REACT Registry, 25 Pharmacoepidemiology & Drug Safety 196 (2016).

[85] Shang-Chen Yang et al., The Epidemiology of Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis in China, 2018 J. Immunology Rsch. 1.

[86] "PubMed is a free resource supporting the search and retrieval of biomedical and life sciences literature . . . . The PubMed database contains more than 34 million citations and abstracts of biomedical literature." Nat'l Libr. Med., Nat'l Ctr. for Biotechnology Info., PubMed Overview, https://pubmed.ncbi.nlm.nih.gov/about/ (last visited Aug. 11, 2022).

[87] Ms. Mai was prescribed 300 mg per day. Pet. Ex. 4 at 20; Pet. Ex. 23 at 3.

"[p]atients with asymptomatic hyperuricemia and renal or cardiovascular disease had statistically significant[] increased risk of allopurinol hypersensitivity" and "mortality." Id. The authors warned that physicians should use caution when prescribing allopurinol to those with risk factors and should "consider the potential risks of fatal adverse reactions." Id.

As explained by Dr. He, "compared to the commonly reported cases of SJS/TEN caused by allopurinol, alleged vaccination associated SJS/TEN cases are limited to case reports." Resp. Ex. C at 4. He opined that "case reports do not establish any causal relation between vaccination and disease development. Most importantly, there is not a single case report on Tdap and shingles vaccines associated with SJS/TEN despite the fact that millions of Tdap and shingles vaccines have been administered worldwide." Id.

Dr. He opined that not only did Ms. Mai receive allopurinol, but that she was also "at high risk" due the fact that she was female, older than age 60, and her initial allopurinol dose was 300 mg per day. Resp. Ex. C at 4. He concluded that considering all of these facts, "it is more likely than not that Ms. Mai's SJS/TEN was caused by the allopurinol she took on June 18, 2015." Id.

iv. Althen Prong Three

Regarding Prong Three, Dr. He did not rebut Dr. Gershwin's opinion that a hypersensitivity reaction could occur within four to five days following administration of an offending agent. Instead, he opined that the development of Ms. Mai's SJS/TEN occurred within the time frame described in the medical literature as appropriate for allopurinol to be the offending agent.

Dr. He explained that "Ms. Mai's disease development had two critical time points. The first time point was August 6, 2015 when Ms. Mai had an itchy rash near and around her eyes and was diagnosed [with] dermatitis. This was exactly 7 weeks after her beginning use of allopurinol on June 18, 2015." Resp. Ex. C at 4. Dr. He found "no evidence to rule out that this was de facto the beginning of Ms. Mai's SJS/TEN." Id. "[T]he second time point [was] August 15, 2015," which Dr. He noted is the date that Dr. Gershwin recognized as onset. Id. This date was "8 weeks and 2 days from [Ms. Mai] beginning use of allopurinol on June 18, 2015," and Dr. He stated that Ms. Mai's "[a]llopurinol induced SJS/TEN did occur more than 8 weeks [] after the beginning of the drug use." Id.

As for delayed onset of SJS/TEN occurring more than eight weeks after initiation of allopurinol, Dr. He cited Nguyen et al. Resp. Ex. C at 4 (citing Resp. Ex. C, Tab 5). The authors defined "time to onset" as "the time interval from the start of administration of the suspected drug through to the onset of an [adverse drug reaction]." Resp. Ex. C, Tab 5 at 2. Time to onset for the medications described in the study ranged from one to four days (64.3%), five to 28 days (31.4%), 29 to 56 days (3.4%), and greater than 56 days (0.8%). Id. at 4 tbl.1. Of patients with SJS/TEN, the time to onset ranged from one to four days (49.3%), five to 28 days (42.5%), 29 to 56 days (7.7%), and greater than 56 days (0.5%). Id. The onset ranges included all suspected drugs, including antibiotics, carbamazepine, paracetamol, and allopurinol, and were not broken down by specific medication. Id. at 4 tbl.1, 5, 5 tbl.2. Allopurinol accounted for 15 of the 136

cases (11.03%) of SJS/TEN. Id. at 5 tbl.2. Based on this study, Dr. He opined that SJS/TEN caused by allopurinol can occur more than 8 weeks after initiation of the medication. Resp. Ex. C at 4.

IV. DISCUSSION

A. Standards for Adjudication

The Vaccine Act was established to compensate vaccine-related injuries and deaths. § 10(a). "Congress designed the Vaccine Program to supplement the state law civil tort system as a simple, fair and expeditious means for compensating vaccine-related injured persons. The Program was established to award 'vaccine-injured persons quickly, easily, and with certainty and generosity.'" Rooks v. Sec'y of Health & Hum. Servs., 35 Fed. Cl. 1, 7 (1996) (quoting H.R. Rep. No. 908 at 3, reprinted in 1986 U.S.C.C.A.N. at 6287, 6344).

Petitioner's burden of proof is by a preponderance of the evidence. § 13(a)(1). The preponderance standard requires a petitioner to demonstrate that it is more likely than not that the vaccine at issue caused the injury. Moberly v. Sec'y of Health & Hum. Servs., 592 F.3d 1315, 1322 n.2 (Fed. Cir. 2010). Proof of medical certainty is not required. Bunting v. Sec'y of Health & Hum. Servs., 931 F.2d 867, 873 (Fed. Cir. 1991). Petitioner need not make a specific type of evidentiary showing, i.e., "epidemiologic studies, rechallenge, the presence of pathological markers or genetic predisposition, or general acceptance in the scientific or medical communities to establish a logical sequence of cause and effect." Capizzano v. Sec'y of Health & Hum. Servs., 440 F.3d 1317, 1325 (Fed. Cir. 2006). Instead, Petitioner may satisfy her burden by presenting circumstantial evidence and reliable medical opinions. Id. at 1325-26.

In particular, Petitioner must prove that the vaccine was "not only [the] but-for cause of the injury but also a substantial factor in bringing about the injury." Moberly, 592 F.3d at 1321 (quoting Shyface v. Sec'y of Health & Hum. Servs., 165 F.3d 1344, 1352-53 (Fed. Cir. 1999)); see also Pafford v. Sec'y of Health & Hum. Servs., 451 F.3d 1352, 1355 (Fed. Cir. 2006). The received vaccine, however, need not be the predominant cause of the injury. Shyface, 165 F.3d at 1351. A petitioner who satisfies this burden is entitled to compensation unless Respondent can prove, by a preponderance of the evidence, that the vaccinee's injury is "due to factors unrelated to the administration of the vaccine." § 13(a)(1)(B). However, if a petitioner fails to establish a prima facie case, the burden does not shift. Bradley v. Sec'y of Health & Hum. Servs., 991 F.2d 1570, 1575 (Fed. Cir. 1993).

"Regardless of whether the burden ever shifts to the [R]espondent, the special master may consider the evidence presented by the [R]espondent in determining whether the [P]etitioner has established a prima facie case." Flores v. Sec'y of Health & Hum. Servs., 115 Fed. Cl. 157, 162-63 (2014); see also Stone v. Sec'y of Health & Hum. Servs., 676 F.3d 1373, 1379 (Fed. Cir. 2012) ("[E]vidence of other possible sources of injury can be relevant not only to the 'factors unrelated' defense, but also to whether a prima facie showing has been made that the vaccine was a substantial factor in causing the injury in question."); de Bazan v. Sec'y of Health & Hum. Servs., 539 F.3d 1347, 1353 (Fed. Cir. 2008) ("The government, like any defendant, is permitted to offer evidence to demonstrate the inadequacy of the [P]etitioner's evidence on a requisite

element of the [P]etitioner's case-in-chief."); Pafford, 451 F.3d at 1358-59 ("[T]he presence of multiple potential causative agents makes it difficult to attribute 'but for' causation to the vaccination. . . . [T]he Special Master properly introduced the presence of the other unrelated contemporaneous events as just as likely to have been the triggering event as the vaccinations.").

B. Factual Issues

A petitioner must prove, by a preponderance of the evidence, the factual circumstances surrounding her claim. § 13(a)(1)(A). To resolve factual issues, the special master must weigh the evidence presented, which may include contemporaneous medical records and testimony. See Burns v. Sec'y of Health & Hum. Servs., 3 F.3d 415, 417 (Fed. Cir. 1993) (explaining that a special master must decide what weight to give evidence including oral testimony and contemporaneous medical records). Contemporaneous medical records, "in general, warrant consideration as trustworthy evidence." Cucuras v. Sec'y of Health & Hum. Servs., 993 F.2d 1525, 1528 (Fed. Cir. 1993). But see Kirby v. Sec'y of Health & Hum. Servs., 997 F.3d 1378, 1382 (Fed. Cir. 2021) (rejecting the presumption that "medical records are accurate and complete as to all the patient's physical conditions"); Shapiro v. Sec'y of Health & Hum. Servs., 101 Fed. Cl. 532, 538 (2011) ("[T]he absence of a reference to a condition or circumstance is much less significant than a reference which negates the existence of the condition or circumstance." (quoting Murphy v. Sec'y of Health & Hum. Servs., 23 Cl. Ct. 726, 733 (1991), aff'd per curiam, 968 F.2d 1226 (Fed. Cir. 1992))), recons. den'd after remand, 105 Fed. Cl. 353 (2012), aff'd mem., 503 F. App'x 952 (Fed. Cir. 2013).

There are situations in which compelling testimony may be more persuasive than written records, such as where records are deemed to be incomplete or inaccurate. Campbell v. Sec'y of Health & Hum. Servs., 69 Fed. Cl. 775, 779 (2006) ("[L]ike any norm based upon common sense and experience, this rule should not be treated as an absolute and must yield where the factual predicates for its application are weak or lacking."); Lowrie v. Sec'y of Health & Hum. Servs., No. 03-1585V, 2005 WL 6117475, at *19 (Fed. Cl. Spec. Mstr. Dec. 12, 2005) ("[W]ritten records which are, themselves, inconsistent, should be accorded less deference than those which are internally consistent." (quoting Murphy, 23 Cl. Ct. at 733)). Ultimately, a determination regarding a witness's credibility is needed when determining the weight that such testimony should be afforded. Andreu v. Sec'y of Health & Hum. Servs., 569 F.3d 1367, 1379 (Fed. Cir. 2009); Bradley, 991 F.2d at 1575.

Despite the weight afforded to medical records, special masters are not bound rigidly by those records in determining onset of a petitioner's symptoms. Valenzuela v. Sec'y of Health & Hum. Servs., No. 90-1002V, 1991 WL 182241, at *3 (Fed. Cl. Spec. Mstr. Aug. 30, 1991); see also Eng v. Sec'y of Health & Hum. Servs., No. 90-1754V, 1994 WL 67704, at *3 (Fed. Cl. Spec. Mstr. Feb. 18, 1994) ("[Section 13(b)(2)] must be construed so as to give effect also to § 13(b)(1) which directs the special master or court to consider the medical records (reports, diagnosis, conclusions, medical judgment, test reports, etc.), but does not require the special master or court to be bound by them." (emphasis omitted)).

C. Causation

To receive compensation through the Program, Petitioner must prove either (1) that Ms. Mai suffered a "Table Injury"—i.e., an injury listed on the Vaccine Injury Table—corresponding to a vaccine that she received, or (2) that Ms. Mai suffered an injury that was actually caused by a vaccination. See §§ 11(c)(1), 13(a)(1)(A); Capizzano, 440 F.3d at 1319-20. Because Petitioner does not allege Ms. Mai suffered a Table Injury, she must prove a vaccine Ms. Mai received caused her injury. To do so, Petitioner must establish, by preponderant evidence: "(1) a medical theory causally connecting the vaccination and the injury; (2) a logical sequence of cause and effect showing that the vaccination was the reason for the injury; and (3) a showing of a proximate temporal relationship between vaccination and injury." Althen, 418 F.3d at 1278.

The causation theory must relate to the injury alleged. Petitioner must provide a sound and reliable medical or scientific explanation that pertains specifically to this case, although the explanation need only be "legally probable, not medically or scientifically certain." Knudsen v. Sec'y of Health & Hum. Servs., 35 F.3d 543, 543, 548-49 (Fed. Cir. 1994). Petitioner cannot establish entitlement to compensation based solely on his assertions; rather, a vaccine claim must be supported either by medical records or by the opinion of a medical doctor. § 13(a)(1). In determining whether Petitioner is entitled to compensation, the special master shall consider all materials in the record, including "any . . . conclusion, [or] medical judgment . . . which is contained in the record regarding . . . causation." § 13(b)(1)(A). The undersigned must weigh the submitted evidence and the testimony of the parties' proffered experts and rule in Petitioner's favor when the evidence weighs in her favor. See Moberly, 592 F.3d at 1325-26 ("Finders of fact are entitled—indeed, expected—to make determinations as to the reliability of the evidence presented to them and, if appropriate, as to the credibility of the persons presenting that evidence."); Althen, 418 F.3d at 1280 (noting that "close calls" are resolved in Petitioner's favor).

V. DIAGNOSIS ANALYSIS

As Federal Circuit precedent establishes, in certain cases it is appropriate to determine the nature of an injury before engaging in the Althen analysis. Broekelschen v. Sec'y of Health & Hum. Servs., 618 F.3d 1339, 1346 (Fed. Cir. 2010). Since "each prong of the Althen test is decided relative to the injury[,]" determining facts relating to the claimed injury can be significant in a case where diagnosis is not clear. Id. Here, Petitioner's expert opines that Ms. Mai's appropriate diagnosis was SJS/TEN. Respondent's expert, Dr. Boos, disagrees and asserts that DRESS is the correct diagnosis. The undersigned need not resolve which of these specific illnesses Ms. Mai suffered to resolve causation. Instead, the undersigned finds that Ms. Mai had a severe cutaneous adverse reaction (SCAR), which is an umbrella diagnosis that encompasses both SJS/TEN and DRESS.

A brief review of Ms. Mai's relevant medical records shows that SJS/TEN and DRESS were all considered as possible diagnoses throughout her clinical course. When first admitted to the hospital, Dr. Sanghavi examined Ms. Mai on September 3, 2015, and considered but ultimately rejected the diagnoses of SJS and DRESS. Because Ms. Mai had no oral lesions and no desquamation, Dr. Sanghavi did not believe that Ms. Mai had SJS. Dr. Sanghavi rejected

DRESS as the diagnosis because Ms. Mai did not give a history of starting any new medication within the prior two to six weeks. During the same hospitalization, on September 4, 2015, Ms. Mai was seen by Dr. Lavkan who did not believe that she had SJS because her mucous membranes were not involved. A biopsy done during the first hospital admission was inconclusive.

The only time that Ms. Mai was seen by a dermatologist was on September 29, 2015, when she saw Dr. Luu, who diagnosed Ms. Mai with TEN-like reaction.

Moving forward in time, when Ms. Mai was readmitted to the hospital on December 19, 2015, her case was discussed with an outside dermatologist who reviewed photographs. That unknown dermatologist did not believe the photos were consistent with SJS, but believed the correct diagnosis was exfoliative dermatitis. Two days later, however, on December 21, the infectious disease physician, Dr. Charney, diagnosed Ms. Mai with SJS. Ms. Mai's death certificate identifies exfoliative dermatitis as a significant condition contributing to her death. Neither SJS nor DRESS were noted on her death certificate.

In summary, the treating physicians contemplated SJS, TEN, and DRESS as possible diagnoses but it does not appear that there was ever any agreement as to the proper diagnosis.

A number of the medical articles filed by Dr. Gershwin speak to the fact that diagnosis of the specific type of SCAR can be difficult, if not impossible. Casagranda et al., for example, noted that while SJS/TEN and DRESS are different conditions, they share some of the same features. Kim et al. also emphasized the "clinical similarities" between SJS/TEN and DRESS, and explained such similarities "can cause confusion in diagnosis." Pet. Ex. 25-E at 1. Wolf et al. addressed the same concerns expressed by Kim et al., and found "[a] case that precisely fit[] the definition of [SJS and DRESS]." Pet. Ex. 25-H at 3. Similarly, Magbri and Seth noted that SJS, TEN, and DRESS "have many histological and biological features in common," and such overlap "mak[es] accurate diagnosis on clinical grounds almost impossible." Pet. Ex. 25-F at 1. Teraki et al. likewise noted the "confusion in the diagnosis of []DRESS syndrome vs. [SJS]/[TEN]." Pet. Ex. 25-G at 1.

Furthermore, overlap between these various clinical entities also appears to occur, making an accurate diagnosis difficult, if not, impossible. See, e.g., Pet. Ex. 13-B at 2; Pet. Ex. 25-F at 1 (noting that diagnosis of SJS, TEN, and DRESS "is mainly based on clinical grounds, and overlap between the various clinical entities do occur[,] making accurate diagnosis on clinical grounds almost impossible").

Lastly, it is not necessary to make a diagnosis of a specific type of SCAR in order for the undersigned to resolve the issue of causation, as the case law illustrates. The Federal Circuit has made clear that "identifying [the Petitioner's] injury is a prerequisite" to the Althen analysis. Broekelschen, 618 F.3d at 1346. However, it is not necessary to diagnose an exact condition. Astle v. Sec'y of Health & Hum. Servs., No. 14-369V, 2018 WL 2682974, at *19 (Fed. Cl. Spec. Mstr. May 15, 2018). In Lombardi, the Federal Circuit explained that "[t]he function of a special master is not to diagnose vaccine-related injuries, but instead to determine based on the record evidence as a whole and the totality of the case, whether it has been shown by a preponderance

of the evidence that a vaccine caused the [P]etitioner's injury." Lombardi v. Sec'y of Health & Hum. Servs., 656 F.3d 1343, 1351 (Fed. Cir. 2011) (internal quotation marks omitted) (quoting Andreu, 569 F.3d at 1382); see also Broekelschen, 618 F.3d at 1346 (citing Kelley v. Sec'y of Health & Hum. Servs., 68 Fed. Cl. 84, 100-01 (2005) for the proposition that "the [P]etitioner [is] not required to categorize his injury where the two possible diagnoses [are] 'variants of the same disorder'"). Furthermore, neither the Vaccine Act nor Althen burdens Petitioner with establishing a specific diagnosis. See Kelley, 68 Fed. Cl. at 100 ("The Vaccine Act does not require [P]etitioners coming under the non-Table injury provision to categorize their injury; they are merely required to show that the vaccine in question caused them injury—regardless of the ultimate diagnosis.").

Taking into account the fact that Ms. Mai's treating physicians struggled to diagnose her specific illness, and the opinions voiced by Dr. Gershwin and the authors of the relevant medical literature about the difficulties in making a diagnosis, the undersigned finds that it is not possible, on this record, to determine Ms. Mai's specific diagnosis. The undersigned finds that the evidence does, however, establish that Ms. Mai had a severe cutaneous adverse reaction, or SCAR. This umbrella diagnosis encompasses all of the conditions at issue, SJS/TEN and DRESS.

VI. CAUSATION ANALYSIS

A. Althen Prong One

Under Althen Prong One, Petitioner must set forth a medical theory explaining how the received vaccine could have caused the sustained injury. Andreu, 569 F.3d at 1375; Pafford, 451 F.3d at 1355-56. Petitioner's theory of causation need not be medically or scientifically certain, but it must be informed by a "sound and reliable" medical or scientific explanation. Boatmon v. Sec'y of Health & Hum. Servs., 941 F.3d 1351, 1359 (Fed. Cir. 2019); see also Knudsen, 35 F.3d at 548; Veryzer v. Sec'y of Health & Hum. Servs., 98 Fed. Cl. 214, 223 (2011) (noting that special masters are bound by both § 13(b)(1) and Vaccine Rule 8(b)(1) to consider only evidence that is both "relevant" and "reliable"). If Petitioner relies upon a medical opinion to support her theory, the basis for the opinion and the reliability of that basis must be considered in the determination of how much weight to afford the offered opinion. See Broekelschen, 618 F.3d 1339 at 1347 ("The special master's decision often times is based on the credibility of the experts and the relative persuasiveness of their competing theories."); Perreira v. Sec'y of Health & Hum. Servs., 33 F.3d 1375, 1377 n.6 (Fed. Cir. 1994) (stating that an "expert opinion is no better than the soundness of the reasons supporting it" (citing Fehrs v. United States, 620 F.2d 255, 265 (Ct. Cl. 1980))).

The parties' medical literature does not identify vaccines as "high risk drugs" associated with SCARs. In Borchers et al., an article co-authored by Dr. Gershwin, Petitioner's expert, the authors identify drugs commonly associated with SJS/TEN, and while allopurinol was on the list, vaccines were not. See Pet. Ex. 11-C at 5 tbl.1. Chahal et al. conducted a literature review and identified 29 articles about EM, SJS, and TEN reported after vaccination. The majority (23) were case reports. Pet. Ex. 11-D at 3. In many cases, several vaccines were administered, confounding the issue of causation. There were only three reports dealing with the DPT vaccine

and two with the DT vaccine. In all of those cases, the patients were diagnosed with EM. And in three of the reports, the children received a DPT or DT vaccine combined with other vaccines. A Tdap-related SCAR was reported by Chopra et al. There, however, the illness was attributed to the smallpox vaccine. Pet. Ex. 11-I at 1, 4. Moreover, all of the patients were diagnosed with EM, and not a more severe form of illness such as SJS/TEN or DRESS. In summary, there is scant evidence in the medical literature of a causal association between the Tdap vaccine and SCARs.

In a more recent article published in 2020 by Su et al., VAERS reports were analyzed. The authors noted one case of a male with EM after the DTaP vaccine who later developed EM after a booster. Resp. Ex. H, Tab 17 at 3. Overall, in the 984 cases of EM, 89 cases of SJS, 6 cases of SJS/TEN, and 7 cases of TEN, they found 199 cases where DTaP was administered, and in only 17 of those cases was DTaP administered alone. Id. at 1, 3, 4 tbl.3. The multiple administrations of vaccines confounds the results. None of the reports involving death were associated with the DTaP vaccine. Id. at 3. Moreover, in the six deaths reported, four reports noted that the patients had also received medications "known to cause SJS or TEN." Id. at 5.

Similarly, in another 2020 article, Grazina et al. reviewed scientific databases regarding vaccines, including the tetanus vaccine and the DTaP-IPV vaccine, and concluded that "[n]one of the [] studies reported statistically significant associations between vaccination and [SJS]." Resp. Ex. H, Tab 3 at 1.

The mechanism of delayed hypersensitivity as described by Dr. Gershwin appears to be well-documented and the Respondent's experts did not rebut it as to vaccines per se. Instead, Respondent's experts opined that there was insufficient evidence to establish that the specific vaccine in this case, the Tdap vaccine, could cause a SCAR.

Given all of the evidence, and for the reasons described above, the undersigned finds that there is not preponderant evidence that the Tdap vaccine can cause a SCAR. Thus, Petitioner has failed to prove Althen Prong One by preponderant evidence.

B. Althen Prong Two

Under Althen Prong Two, Petitioner must prove by a preponderance of the evidence that there is a "logical sequence of cause and effect showing that the vaccination was the reason for the injury." Capizzano, 440 F.3d at 1324 (quoting Althen, 418 F.3d at 1278). "Petitioner must show that the vaccine was the 'but for' cause of the harm . . . or in other words, that the vaccine was the 'reason for the injury.'" Pafford, 451 F.3d at 1356 (internal citations omitted).

In evaluating whether this prong is satisfied, the opinions and views of the vaccinee's treating physicians are entitled to some weight. Andreu, 569 F.3d at 1367; Capizzano, 440 F.3d at 1326 ("[M]edical records and medical opinion testimony are favored in vaccine cases, as treating physicians are likely to be in the best position to determine whether a 'logical sequence of cause and effect show[s] that the vaccination was the reason for the injury.'" (quoting Althen, 418 F.3d at 1280)). Medical records are generally viewed as trustworthy evidence, since they are created contemporaneously with the treatment of the vaccinee. Cucuras, 993 F.2d at 1528.

Petitioner need not make a specific type of evidentiary showing, i.e., "epidemiologic studies, rechallenge, the presence of pathological markers or genetic predisposition, or general acceptance in the scientific or medical communities to establish a logical sequence of cause and effect." Capizzano, 440 F.3d at 1325. Instead, Petitioner may satisfy her burden by presenting circumstantial evidence and reliable medical opinions. Id. at 1325-26.

Since Petitioner has failed to prove that the Tdap vaccine can cause a SCAR, it stands to reason that she cannot prevail on Prong Two. However, even if Petitioner had proven Althen Prong One, the undersigned finds that Petitioner has failed to prove Althen Prong Two by preponderant evidence.

In determining whether Petitioner has put forth preponderant evidence of Althen Prong Two, the undersigned generally takes into consideration the opinions of the treating physicians. Treating physician statements are typically "favored" as treating physicians "are likely to be in the best position to determine whether a 'logical sequence of cause and effect show[s] that the vaccination was the reason for the injury.'" Capizzano, 440 F.3d at 1326 (quoting Althen, 418 F.3d at 1280). However, no treating physician's views bind the special master, per se; rather, their views should be carefully considered and evaluated. § 13(b)(1); Snyder v. Sec'y of Health & Hum. Servs., 88 Fed. Cl. 706, 746 n.67 (2009). "As with expert testimony offered to establish a theory of causation, the opinions or diagnoses of treating physicians are only as trustworthy as the reasonableness of their suppositions or bases." Welch v. Sec'y of Health & Hum. Servs., No. 18-494V, 2019 WL 3494360, at *8 (Fed. Cl. Spec. Mstr. July 2, 2019). Each opinion from a treating physician should be weighed against other, contrary evidence in the record. Hibbard v. Sec'y of Health & Hum. Servs., 100 Fed. Cl. 742, 749 (2011), aff'd, 698 F.3d 1355 (Fed. Cir. 2012); Caves v. Sec'y of Health & Hum. Servs., 100 Fed. Cl. 119, 136 (2011), aff'd, 463 F. App'x 932 (Fed. Cir. 2012); Veryzer v. Sec'y of Health & Hum. Servs., No. 06-522V, 2011 WL 1935813, at *17 (Fed. Cl. Spec. Mstr. Apr. 29, 2011), mot. for rev. denied, 100 Fed. Cl. 344 (2011), aff'd without op., 475 F. App'x 765 (Fed. Cir. 2012).

Here, there is no evidence to suggest that the physicians who treated Ms. Mai during her first hospital admission in September 2015 were aware that she had been prescribed allopurinol and began taking it on or about June 18, 2015. The evidence shows that Dr. Nguyen prescribed a 90-day prescription for allopurinol 300 mg on June 18, 2015. The prescription was filled, paid for, and picked up from the pharmacy on the same day, June 18. Based on the affidavit of Petitioner, it would have been Ms. Mai's practice to take the medication prescribed by her doctor. Thus, Ms. Mai would have taken the medicine from June 18, 2015, until she was taken by ambulance to the hospital on September 2, 2015.

When EMS personnel came to Ms. Mai's house on September 2, 2015, they collected her medication and took it to the hospital. However, the EMS records do not identify allopurinol as one of Ms. Mai's current medications. Additionally, the ED and hospital records did not identify allopurinol as a current medication. Petitioner, Ms. Mai's daughter, provided a declaration. In the declaration, she avers that she did not know her mother was on allopurinol. Therefore, she could not have provided that information to the healthcare providers at the hospital. There is no mention of allopurinol in the admitting records, the admitting history, or in the records of the nurses or the physicians. Allopurinol was not ordered or administered as a medication for Ms.

Mai while she was in the hospital. If the physicians did not know that Ms. Mai had been taking allopurinol, they would not have considered it as a cause of her drug reaction.

The medical literature filed by both parties is replete with reports showing that allopurinol is a common cause of SCARs. Unfortunately, there is no evidence that the healthcare providers who cared for Ms. Mai knew she was taking allopurinol. They believed that the only new medications introduced within two to six weeks prior to hospitalization were her vaccinations administered on August 11, 2015.

For example, Dr. Sanghavi, on September 3, 2015, wrote "that approximately nine days ago [Ms. Mai] received her [Tdap] vaccination," and "[a]bout 4 days later, she developed a salmon colored blanching rash." Pet. Ex. 7 at 67. Dr. Sanghavi also noted "[Ms. Mai's] time course [of a] few days after her vaccination would be consistent with a serum sickness like illness and her 28% eosinophilia on her CBC would also be consistent with this" and Dr. Sanghavi considered "allergic interstitial nephritis." Id. at 69. Dr. Studemeister, an infectious disease specialist, performed a consult on September 3, 2015 and wrote, "possible reaction to recent vaccination." Pet. Ex. 19 at 852. Also on September 3, 2015, a progress note by Dr. Aggu-Sher noted that the rash had an "[u]nclear etiology. ? from recent vaccinations." Id. at 853. Dr. Lavkan, on September 4, noted "[d]ifferential is broad but at the top comes allergic reaction to the vaccine she received or the components of it." Id. at 861. In the discharge paperwork from September 7, 2015, Dr. Zhang wrote the discharge diagnosis as "[s]evere dermatitis, most likely reaction to the vaccine." Id. at 65. Then, on September 29, 2015, Ms. Mai's dermatologist, Dr. Luu, found Ms. Mai's condition was "possibly [seco]ndary to vaccination for shingles and tetanus." Pet. Ex. 4 at 9. On October 16, 2015, Ms. Mai visited Dr. Huy Nguyen, who wrote "[t]hree days [after vaccination], she developed severe rashes." Id. at 6.

However, the assessments of the physicians above who documented an association between Ms. Mai's Tdap vaccination and her illness appear to be based on incomplete information. None of the physicians documented that Ms. Mai was taking allopurinol, a common culprit of SCARs. Without this critical piece of evidence, the opinions of the physicians stating that a vaccine played a role in Ms. Mai's illness are based on a flawed history, and are therefore not persuasive.

Respondent argues that allopurinol was the cause of Ms. Mai's illness, or an alternative factor unrelated to her Tdap vaccination. The causal role of allopurinol, however, is not settled. While it appears that Ms. Mai took allopurinol, the dates that she took it are not entirely clear. Additionally, Dr. Nguyen, who ordered the allopurinol, did not recognize allopurinol as the cause of her illness, and in fact, he refilled the prescription for her. The fact that her primary care physician did not attribute her illness to allopurinol and refilled the prescription raises a question about whether it played a causal role. Further, Ms. Mai was also taking sitagliptin for her diabetes, which Respondent's expert noted has also been associated with adverse drug reactions. See, e.g., Resp. Ex. H, Tab 15 at 2 (noting a link between sitagliptin and DRESS).

The undersigned will not step into the role of a physician or render a causal opinion based on hindsight. Instead, the undersigned finds that allopurinol may have been an alternative factor, and takes this evidence into consideration on the issue of whether Petitioner has proven Althen

Prong Two by preponderant evidence. See Flores, 115 Fed. Cl. at 162-63 ("Regardless of whether the burden ever shifts to the [R]espondent, the special master may consider the evidence presented by the [R]espondent in determining whether the [P]etitioner has established a prima facie case."); Stone, 676 F.3d at 1379 ("[E]vidence of other possible sources of injury can be relevant not only to the 'factors unrelated' defense, but also to whether a prima facie showing has been made that the vaccine was a substantial factor in causing the injury in question."); de Bazan, 539 F.3d at 1353 ("The government, like any defendant, is permitted to offer evidence to demonstrate the inadequacy of the [P]etitioner's evidence on a requisite element of the [P]etitioner's case-in-chief."); Pafford, 451 F.3d at 1358-59 ("[T]he presence of multiple potential causative agents makes it difficult to attribute 'but for' causation to the vaccination. . . . [T]he Special Master properly introduced the presence of the other unrelated contemporaneous events as just as likely to have been the triggering event as the vaccinations."). However, the undersigned does not find that the evidence is sufficient to establish, more likely than not, that allopurinol was the cause of Ms. Mai's SCAR. Thus, there is not preponderant evidence that Ms. Mai's injury was "due to factors unrelated to the administration of the vaccine." § 13(a)(1)(B).

For the above reasons, the undersigned finds that Petitioner has failed to prove by preponderant evidence that the Tdap vaccine caused Ms. Mai's illness. Thus, Petitioner has failed to prove Althen Prong Two.

C. Althen Prong Three

Althen Prong Three requires Petitioner to establish a "proximate temporal relationship" between the vaccination and the injury alleged. Althen, 418 F.3d at 1281. That term has been defined as a "medically acceptable temporal relationship." Id. Petitioner must offer "preponderant proof that the onset of symptoms occurred within a timeframe which, given the medical understanding of the disease's etiology, it is medically acceptable to infer causation-in-fact." de Bazan, 539 F.3d at 1352. The explanation for what is a medically acceptable time frame must also coincide with the theory of how the relevant vaccine can cause the injury alleged (under Althen Prong One). Id.; Koehn v. Sec'y of Health & Hum. Servs., 773 F.3d 1239, 1243 (Fed. Cir. 2014); Shapiro, 101 Fed. Cl. at 542.

The experts generally agree as to the range of onset. Dr. Gershwin places onset of Ms. Mai's illness on August 15, 2015, when "she developed a salmon colored blanching rash" four days post-vaccination. Pet. Ex. 7 at 67. Dr. Boos opined that onset occurred between August 6, 2015, "when [Ms. Mai] first reported an itchy macular rash to her face," and August 27, 2015, "when [Ms. Mai] re-presented with fevers, fatigue[,] and a macular rash." Resp. Ex. A at 8. And Dr. He opined that onset was either August 6, 2015, due to the itchy rash near and around her eyes and diagnosis of dermatitis, or August 15, 2015, that date in which Dr. Gershwin recognized as Ms. Mai's onset.

As described by Borchers et al., co-authored by Dr. Gershwin, a delay of four to 28 days is the "[m]ost suspicious" time frame for onset in SJS/TENS. Pet. Ex. 11-C at 5. Regarding DRESS, onset is "typically [] within 2 months of first exposure to the inciting agent." Resp. Ex. A at 6 (citing Resp. Ex. A, Tab 5 at 2).

Here, the undersigned finds that onset of Ms. Mai's hypersensitivity reaction occurred approximately August 15, 2015, which is a medically appropriate time frame given Petitioner's proposed theory of delayed hypersensitivity. Thus, the undersigned finds that Petitioner has proven Althen Prong Three by preponderant evidence. However, temporal association alone is insufficient for Petitioner to show vaccine causation for Ms. Mai's alleged injury, and thus, Petitioner is not entitled to compensation.

VII. CONCLUSION

As stated earlier, this is a very tragic case. The undersigned extends her sympathy to Petitioner and her family for their loss. The undersigned's Decision, however, is not based on sympathy, but based on the evidence.

For the reasons discussed above, the undersigned finds that Petitioner has failed to establish by preponderant evidence that Ms. Mai's Tdap vaccine caused her illness. Therefore, the petition shall be dismissed.

IT IS SO ORDERED.

s/Nora Beth Dorsey
Nora Beth Dorsey
Special Master